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THE RETENTION OF ELECTROLYTE DURING RECOVERY FROM SEVERE DEHYDRATION DUE TO DIARRHEA

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PREVIOUS studies of the changes in the composition of the body produced by diarrhea have considered the evidences of loss of intracellular water and electrolyte as a result of a breakown of the tissues which is not readily reversible. This interpretation was largely a consequence of the prevailing concepts of the structure of intracellular and extracellular fluids in which the peculiar distribution of electrolyte was considered to depend largely on the exclusion of sodium and chloride from the cells and on the relative impermeability of cellular membranes to potassium. In the past ten years these views have been disproved. It is now clear that intracellular fluids contain appreciable amounts of sodium and chloride, and that potassium readily crosses the cellular membranes. Normally the muscles contain a small amount of intracellular sodium which has been shown to be transferred to the extracellular fluids in one type of acidosis.[1, 2] Under certain circumstances considerable amounts of potassium are lost from the intracellular phase of muscle and are replaced by almost equivalent amounts of sodium. This change has been shown to occur as a consequence of diets low in potassium,[3-6] after injections of desoxycorticosterone acetate,[4, 7] in response to certain steroids,[8] and following prolonged therapy with solutions containing only glucose and sodium chloride.[9, 10] Certain patients with Cushing's syndrome and refractory alkalosis have a deficit of potassium in their muscles.[11, 12] Elsewhere the author[13] has outlined a new framework for the presentation of the disturbances of body water and electrolyte and has developed the concepts which take into account these facts. The present work fits the losses of electrolyte produced by diarrhea into this framework.

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The general plan of the experiments was to obtain the actual retentions of the chief extracellular and intracellular ions during recovery from the dehydration of severe diarrhea. The patients were considered to have recovered when they were taking adequate food and gaining weight for two or more days. In the six cases which will be reported, this criterion was met in all but Cases 3 and 4 and these patients were gaining two days after termination of the study. It was hoped that the gain in weight on normal intake would indicate normal tissue water and electrolyte, and hence that the retentions would equal the deficits at the beginning of the study. It was not expected that tissues consumed as a whole with loss of nitrogen, phosphorus, and potassium would be reconstituted, but it was anticipated that those present in the body would have an essentially normal composition with respect to nitrogen, phosphorus, and potassium; that is, the body would be normal except for the results of starvation. Analyses of the muscles of cats subjected to nine days of starvation do not show any change in the composition of muscle per unit of fat-free solids. As will be pointed out later, the retentions of sodium and chloride are so large that some of the gain in weight must be considered due to overexpansion of the extracellular fluids. Within the cells, the retentions of potassium and phosphorus almost certainly represent true deficits on admission, since excessive retentions of these ions are unlikely and, in experimental animals, have been produced with respect to potassium only by raising the extracellular concentrations to abnormally high levels. However, the experiments provide no criterion by which to judge whether longer periods of observation would have led to even greater retentions before nitrogen, phosphorus, and potassium could be retained in the normal relations to each other.

During the balance studies, the usual therapeutic measures were carried out. In the first four cases, no potassium was given parenterally during the period of fasting, while potassium was given parenterally in the last two cases. The studies, therefore, permit a comparison of the effects of the conventional therapy with the new type which uses potassium salts, parenterally and from the beginning of the therapy directed toward replacement of water and electrolyte.

METHODS

Immediately on selection of the case, blood was taken under mineral oil and the baby placed on a metabolism bed so as to collect urine and feces separately. Urine was preserved with thymol or toluol and collected over the period of time without catheterization. Stool collections were started immediately and the end of each period demarcated by giving a small amount of carmine by mouth. At the end of each period a sample of blood was taken. During the first period nothing was given by mouth, and fluid intake and replacement therapy was instituted by giving a slow intravenous drip of solutions containing sodium chloride, sodium lactate, and glucose in the first four cases and by giving potassium chloride, in addition, in the last two cases. Blood and plasma were also given when indicated on clinical grounds. The exact intakes are given in the tables and the case protocols. During the second period food at submaintenance levels of intake was given, while in the third period maintenance

feeding was given except in Case 4. As noted in the protocols, parenteral fluid was given in Period II of Case 4. Potassium chloride was added to the food during Period II in all but Case 6. The basic food in all cases was a mixture of powdered whole milk and powdered skimmed milk, in order that the mixture have about 2 per cent fat and 3.5 per cent protein. Dextrimaltose equal to 10 per cent of this mixture was added. In Case 3 the dextrimaltose contained sodium chloride, but in the other cases it was free of salt. The food mixture was usually diluted with sufficient water to give adequate fluid intake. The exact intakes are shown in the tables and protocols.

All food, intravenous solutions containing electrolyte, and excreta were analyzed in duplicate on separate aliquots. The intakes of intravenous fluids containing electrolyte were measured by weighing the bottles; glucose solutions were measured by volume. In the last two cases the intakes by mouth were measured by weighing the bottles, but in the first four cases the measurements were by volume. When transfusions were given, only the electrolyte content of the plasma was considered in the balances.

The chemical methods were those in previous use by the author.[1] A glass electrode at 38° C. was used to measure the pH in the first two cases. Unusual values — particularly serum chloride and sodium — were rechecked. A Waring mixer was used for the stools, and aliquots obtained by weighing a well-mixed portion. In all analyses the checks were better than 2 per cent. Excepting the loss of about 50 Gm. of stool in Period II of Case 6, no serious error in the collections is known to have occurred. There was no vomiting in any case and in all but Period II of Case 4, little food was refused.

CALCULATIONS

The tables present the serum concentrations and the balances in the usual manner. The charts show the cumulative balances at the end of each period in intracellular and extracellular fluids. In order to make the different cases comparable, the cumulative balances in the charts were adjusted to balances per 10 kg., using the final body weight in making this calculation. The figures to the right of the charts are estimated normal contents of a 10 kg. child.[13]

The calculations used in constructing the charts have been previously described and applied.[2, 14] In calculating the distribution of the balances, the following assumptions were made: (1) that the concentration of sodium and chloride in extracellular water is measured by that of an ultrafiltrate of serum,* (2) that the initial volume of extracellular water is 20 per cent of the weight on admission, (3) that the balance of chloride represents a change in extracellular chloride only.

Using brackets [ ] to indicate concentrations and parentheses ( ) to indicate amounts, the following equations are self-explanatory.

(Initial extracellular H_2O) [Initial extracellular Cl] = (Initial extracellular Cl)
(Initial extracellular Cl) + (Balance Cl) = (Final extracellular Cl)
(Final extracellular Cl) ÷ [Final extracellular Cl] = (Final extracellular H_2O)
(Initial extracellular H_2O) [Initial extracellular Na] = (Initial extracellular Na)

*The concentration in the ultrafiltrate was derived from the serum concentration of water and electrolyte and an average Donnan factor of 0.96.

(Final extracellular H_2O) [Final extracellular Na] = (Final extracellular Na)
(Final extracellular Na) − (Initial extracellular Na) + (Balance Na) =
(Balance intracellular Na)

The amount of water is expressed in kilograms; the amount of electrolyte in millimoles and the concentrations in millimoles per kilogram of water. Similar equations were set up for potassium, but no correction for extracellular phosphorus was made owing to the lack of determination of the concentrations of serum phosphorus.

Applying these equations gives the shifts of sodium, potassium, and phosphorus into the cells. However, it does not measure the deviations from normal in the composition of the cells. In order to correct for changes in the amount of cytoplasm it was assumed that when cytoplasm is broken down or reconstituted, the balances of nitrogen, phosphorus, and potassium have the same relation to each other as found in muscle. In the case of phosphorus it was assumed that any balance of calcium would be reflected by a change in bone phosphorus which is indicated by the ratio of Ca:P in bone salts. The following equations express these relationships:

P = 2 N + 0.57 Ca predicted balance of phosphorus from the balance of N and Ca
K = 3 N predicted balance of potassium from the balance of nitrogen

Nitrogen balance is expressed in grams; phosphorus and potassium are expressed in millimoles. Urinary calcium was assumed to be negligible in the last five cases since urinary calcium was so low in Case 1.

RESULTS

Tables I to VI give the balances for each period together with the body weight and the time intervals. Table VII gives the serum analyses. The case numbers and dates indicate which analyses were taken at the beginning and the end of each period. The charts (1 to 6) represent the derived data showing the apparent balances in intracellular and extracellular fluids at the end of each period per 10 kg. of body weight. Since the intracellular balances of these charts are corrected for changes in body nitrogen and calcium, they represent deviations from the balances which would be obtained in a normal baby maintaining a normal composition; that is, a positive intracellular balance may be interpreted as due to a deficit in the cells on admission and a negative intracellular balance indicates a presumptive excess on admission. Note that the charts are constructed on a cumulative basis so that the changes in composition represent changes from the composition on admission.

The following protocols show the relevant facts of the histories. All patients were normal at birth and artificially fed on accepted milk mixtures. Stool cultures were made on all patients but only significant findings are reported.

CASE 1.—The patient was a boy, aged 4 weeks, who had been in the care of an orphan asylum. He had been ill for three days starting with transient cyanotic spells, followed by fever on the second day, and many small, loose stools on the third day. He received a hypodermoclysis of 120 c.c. of artificial interstitial salt solution eighteen hours before admission. On admission he was moderately dehydrated but did not have Kussmaul breathing. The baby passed essentially normal stools in the hospital and recovery was rapid and apparently complete at the end of the study.

Period I lasted for 39.5 hours, from 6:30 P.M. on January 18, until 10:00 A.M. on January 20. Nothing was given by mouth. During this period he received 300 c.c. of a mixture of 180 c.c. of isotonic sodium lactate and 150 c.c. of artificial interstitial salt solution; 77 c.c. of blood; and 1,226 c.c. of a mixture of ⅓ physiological saline and ⅔ 10 per cent glucose. His weight changed from 3,500 to 4,060 Gm.

Period II lasted for 49.5 hours, from 10 A.M. January 20, until 11:30 A.M. January 22. On the first day he received 180 c.c. of the milk mixture with 1 Gm. of potassium chloride, and on the second day the same food diluted with 180 c.c. of water. During this period his weight remained 4,060 Gm.

Period III lasted for 72 hours, from 11:30 A.M. January 22, until 11:30 A.M. January 25. During this period the baby took 1,260 c.c. of the milk mixture. The weight changed from 4,060 to 4,300 Gm.

TABLE I. BALANCE IN CASE 1

	SOLIDS Gm.	H_2O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	BODY WEIGHT Kg.
				Period I (39.5 Hours)					
Intake	108	1,526	0.0	83.0	119.0	0.4	0.0	0.0	3.50
Urine		700	2.06	69.6	51.5	7.65	4.5	0.0	
Stools	3.3	12	0.34	0.3	0.5	1.18	0.6	1.4	
Balance			−2.40	13.1	67.0	−8.43	−5.1	−1.4	4.06
				Period II (49.5 Hours)					
Intake	64	476	1.84	35.0	7.9	40.6	9.9	10.3	
Urine		186	0.81	24.1	59.2	16.2	5.7	0.0	
Stools	6	20	0.48	0.0	0.1	1.3	4.2	7.7	
Balance			0.55	10.9	−51.4	23.1	0.0	2.6	4.06
				Period III (72 Hours)					
Intake	227	1,033	6.45	45.4	27.1	49.5	34.5	36.0	
Urine		510	2.28	23.7	10.8	31.1	9.8	0.0	
Stools	15	55	0.78	0.3	0.3	3.5	15.9	34.0	
Balance			3.39	21.4	16.0	13.9	8.8	2.0	4.30

CASE 2.—The patient was a boy, aged 2 months. Owing to whooping cough at home, the boy was cared for in a foster home. Here he received somewhat too much food (160 calories per kilogram) and vomited once or twice daily. Two days before the study, diarrhea as well as vomiting occurred. The diarrhea became worse on skimmed milk and barley flour. The second day he had fever and became sicker. On admission he was vigorous but quite sick and dehydrated. The skin turgor was poor and the eyes sunken. The lips were cyanotic, but there was no Kussmaul breathing. Under treatment the stools remained watery for two days and loose for three days. The stools were yellow and pasty after five days. The baby looked well at the end of the study but did not gain regularly until one week after the end of the balance study.

Period I lasted for 50 hours, from 12:00 noon, April 18, until 2:00 P.M. on April 20. He was given nothing by mouth. Subcutaneous and intravenous fluids were given, containing blood, sodium chloride, sodium bicarbonate, and glucose. The weight changed from 3,850 to 4,300 Gm.

Period II lasted for 3 days, from 2:00 P.M. on April 20, until 2:00 P.M. on April 23. On the first day he received a hypodermoclysis of ⅔ physiological saline and ⅓ 5 per cent glucose (300 c.c.). For the first two days he drank 720 c.c. of 5 per cent glucose with 3 Gm. potassium chloride. On the last day he drank 148 c.c. of the milk mixture plus 1.5 Gm. potassium chloride, and 270 c.c. of water. The weight remained 4,300 Gm.

Period III lasted for 4 days, from 2:00 P.M. April 23, until 2:00 P.M. April 27. On each day the total food intake measured 600 c.c., and contained 1.5 Gm. of added potassium chloride; on the first day, 300 c.c. of the milk mixture were given; and on the last three days, 450 c.c. The baby looked well, but pale, at the end of the study. The weight changed from 4,300 to 4,380 Gm.

TABLE II. BALANCE IN CASE 2

	SOLIDS Gm.	H_2O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	BODY WEIGHT Kg.
				Period I (2 Days 2 Hours)					
Intake	22	1,113	0.0	80.3	120.8	1.8	0.0	0.0	3.85
Urine		160	1.66	9.7	3.3	4.9	9.1		
Stools	8	242	0.61	15.5	15.6	9.7	1.9	1.8	
Balance			−2.27	55.1	101.8	−12.8	−11.0	−1.8	4.30
				Period II (3 Days)					
Intake	44	1,438	0.92	88.4	25.9	68.9	5.4	5.6	
Urine		685	0.91	91.3	40.0	26.5	3.6		
Stools	6	188	0.47	16.8	15.5	8.3	1.4	1.6	
Balance			−0.46	−19.7	−29.6	34.1	0.4	4.0	4.30
				Period III (4 Days)					
Intake	304	2,336	8.35	129.8	37.6	151.0	50.4	52.0	
Urine		1,455	3.26	133.0	48.3	115.8	22.1		
Stools	28	220	1.66	23.1	1.3	11.5	14.8	49.0	
Balance			3.43	−26.3	−12.0	23.7	13.5	3.0	4.38

CASE 3.—The patient was a Negro boy born of a tuberculous mother. The baby was taken care of by an aunt and did not have a positive tuberculin reaction. At the age of 4½ months he was treated in the hospital for ten days for diarrhea and dehydration. Four days before the study, at the age of 7½ months, he had several watery stools. The diarrhea continued at this rate until admission to the hospital. Two days before admission, fever developed and the baby became dull and listless. On admission he was quite sick and dehydrated, with poor skin turgor and sunken eyes. There was no Kussmaul breathing. Although he was not extremely sick, recovery was somewhat slow and the stools were still loose at the end of the study. He gained weight two days later and was discharged well after eleven days of treatment, having gained 800 Gm.

Period I lasted for 38 hours, from 10:00 P.M. on August 20, until 10:00 A.M. on August 22. Nothing was offered by mouth and an intravenous drip gave solutions containing sodium chloride, sodium lactate, and glucose as indicated in the table. The weight changed from 6,050 to 6,100 Gm.

Period II lasted 3 days, from 10:00 A.M. on August 22, until 10:00 A.M. on August 25. To each day's food 1.5 Gm. of potassium chloride were added. On the first day he received 55 calories per kilogram and on the last two days 110 calories per kilogram. The weight changed from 6,100 to 6,350 Gm.

TABLE III. BALANCE IN CASE 3

	SOLIDS Gm.	H_2O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	BODY WEIGHT Kg.
				Period I (38 Hours)					
Intake	59	1,492	0.0	88	132	0.0	0.0	0.0	6.05
Urine		590	1.77	44	44	6.3	7.9		
Stools	19	156	0.73	3	5	12.0	7.5	14.9	
Balance			−2.50	41	83	−18.3	−15.4	−14.9	6.10
				Period II (72 Hours)					
Intake	380	1,909	11.62	143	105	140.0	81.0	57.9	
Urine		672	3.59	79	135	28.7	22.3		
Stools	53	747	0.63	4	17	41.7	15.5	31.5	
Balance			7.40	60	−47	69.6	43.2	26.4	6.35

CASE 4.—The patient was a boy, aged 10½ months. Four days before admission he became irritable and had several loose stools. The next three days he vomited most of his food and had six to eight stools each day. No blood or mucus was noticed in the stools. The day before admission, his temperature was 38° C. and he received sulfadiazine. On ad-

mission he was well developed and nourished, but quite sick and dehydrated. He was greatly prostrated, and out of contact with his environment though he responded to painful stimuli. The skin turgor was poor; the eyes and fontanel sunken. There was questionable otitis media. The eardrums were not incised and did not discharge spontaneously. Under treatment he improved rapidly but remained irrational for two days. The temperature varied between 37 and 39.5° C. during the first five days. He was still apathetic and had loose stools at the end of the study. He improved markedly and gained weight three days after the study. Although pathogenic organisms were not cultured from the stools, the clinical course suggested bacillary dysentery.

Period I lasted for 2 days, from noon on August 21, until noon on August 23. Nothing was given by mouth. By an intravenous drip, he received fluids containing sodium chloride, sodium lactate, glucose, and 200 c.c. of blood. The stools were watery during this period. The weight changed from 1,149 to 1,198 Gm.

Period II lasted for 4 days, from noon on August 23, until noon on August 27. On the first, second, and fourth days he received an intravenous injection of a mixture of ⅔ physiological saline and ⅓ sixth molar sodium lactate. In addition he was given 2 Gm. of potassium chloride in 240 c.c. of 5 per cent glucose by mouth. On the third day, feedings of a milk mixture containing added potassium chloride were taken poorly and discontinued. He received 100 c.c. of blood on this day. Improvement was slow but steady during this period. The weight changed from 11.98 to 12.70 kg.

Period III lasted for three days, from noon on August 27, until noon on August 30. On each day 1.5 Gm. of potassium chloride were added to the milk mixture. On the first two days he received about 20 calories per kilogram and on the last day 40 calories per kilogram. Although the stools remained loose, recovery was satisfactory. He was gaining on adequate calories two days after the study was finished. The weight changed from 12.70 to 11.85 kg.

TABLE IV. BALANCE IN CASE 4

	SOLIDS Gm.	H_2O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	BODY WEIGHT Kg.
				Period I (2 Days)					
Intake	36	1,495	0.0	104	147	0.0	0.0	0.0	11.49
Urine		230	3.35	4	21	6.5	10.6		
Stools	24	538	1.92	25	41	20.2	8.3	6.2	
Balance			−5.27	75	85	−26.7	−18.9	−6.2	11.98
				Period II (4 Days)					
Intake	177	2,540	3.48	258	263	98.0	20.0	20.3	
Urine		670	1.90	144	118	33.2	11.4		
Stools	18	405	1.15	23	37	15.5	7.5	7.5	
Balance			0.43	91	108	49.3	1.1	12.8	12.70
				Period III (3 Days)					
Intake	230	1,699	5.55	99	60	88.2	35.5	34.6	
Urine		430	2.29	101	44	47.8	10.3		
Stools	25	495	1.43	9	20	19.0	11.3	13.5	
Balance			1.33	−11	−4	21.4	13.9	21.1	11.85

CASE 5.—The patient was a boy, aged 3 months. Seven days before admission he started to have watery stools as often as ten times a day. He vomited frequently from the day of onset. The stools were somewhat less frequent during the last four days, but the baby became listless, looked sicker, and his eyes became sunken. On admission he had a temperature of 40° C. and was extremely sick with marked dehydration, diminished skin turgor, sunken eyes and fontanel, and typical Kussmaul breathing. The skin had the typical grayish pallor of shock. Proteus morganii was cultured from the stools. In the hospital his temperature rose to as high as 39 or 40° C. for three days, at which time he looked desperately sick and recovery seemed unlikely. He was discharged well after twenty-three days in the hospital, having gained 800 Gm.

Period I lasted for 97 hours, from 11:00 A.M. on September 4, until noon on September 8. Nothing was given by mouth. By an intravenous drip the following was given: First day, 262 Gm. of a mixture of ⅔ physiological saline and ⅓ isotonic sodium lactate; 519 Gm. of a mixture* of potassium chloride, sodium chloride, and sodium lactate; blood, 50 c.c.; plasma, 50 c.c. Second and third days, potassium chloride 2 Gm., and sodium chloride 3 Gm. in 300 c.c. of water; 450 Gm. of 5 per cent glucose and 261 Gm. of a mixture of ⅔ physiological saline and ⅓ isotonic sodium lactate. Fourth day, potassium chloride 2 Gm., sodium chloride 3 Gm. in 250 c.c. of water, and 180 c.c. of 5 per cent glucose. During this period the stools weighed 195, 282, and 279 grams on first, second, and combined third and fourth days, respectively. The weight changed from 4,860 to 5,200 Gm.

Period II lasted for 5 days, from noon on September 8, until noon on September 13. On the first day he received intravenously 570 c.c. of 5 per cent glucose containing 2 Gm. potassium chloride and 3 Gm. sodium chloride; by mouth he received 270 c.c. of 5 per cent glucose. On the last three days he received a milk mixture made up to 780 c.c. containing about 20 calories per kilogram. To each day's milk, 1.5 Gm. of potassium chloride were added. The weight remained 5,200 Gm.

Period III lasted for 4 days from noon on September 13, until noon on September 17. He was given a milk mixture made up to 720 c.c. which contained for the first two days about 50 calories per kilogram and on the last two days about 90 calories per kilogram. Improvement was steady and the baby was practically recovered at the end of the study. The weight changed from 5,200 to 5,450 Gm.

TABLE V. BALANCE IN CASE 5

	SOLIDS Gm.	H_2O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	BODY WEIGHT Kg.
				Period I (4 Days 1 Hour)					
Intake	53	2,292	0.0	282	279	75.1	0.0	0.0	4.86
Urine		508	3.04	115	84	34.4	11.8		
Stools	19	736	1.42	82	89	25.5	4.1	2.6	
Balance			−4.46	85	106	15.2	−15.9	−2.6	5.20
				Period II (5 Days)					
Intake	229	3,945	3.52	218	159	149.8	23.3	25.7	
Urine		1,656	2.72	126	56	73.2	13.3		
Stools	33	1,036	1.94	83	66	44.0	9.4	17.1	
Balance			−1.17	9	37	32.6	0.6	8.6	5.20
				Period III (4 Days)					
Intake	466	2,497	10.01	67	44	92.5	61.1	62.3	
Urine		1,175	2.41	37	12	39.0	23.3		
Stools	44	494	2.01	23	25	22.9	11.0	40.8	
Balance			5.59	7	7	30.6	26.8	21.5	5.45

CASE 6.—The patient was a boy, aged 11 months. Two weeks before the patient became sick, a sister, aged 3 years, had diarrhea and fever. Four days before admission, the baby had twelve loose stools which were at first yellow and later green. He was given castor oil on this day. The next day he had six watery stools and vomited all food, though he retained a mixture of sugar and water. The vomiting and diarrhea continued until admission. On the third and fourth days, fever was noted, together with increasing weakness and sunken eyes. On admission he was well developed and nourished, but extremely sick. The eyes were sunken and showed a glassy stare. The skin turgor was very poor and the skin had the typical grayish pallor of shock. The stools were not examined microscopically or by guaiac test but contained no gross blood. For the first five days they were practically clear water, with a few flecks of yellowish material that looked like a desquamated membrane. The stools contained an organism belonging culturally to the Flexner group, but the organism was not agglutinated by Flexner serum. The baby had a fever varying from 38 to 40° C. for two

*The mixture of sodium chloride, potassium chloride, and sodium lactate is described in the discussion.

days and looked so sick for three days that recovery seemed unlikely. He had practically recovered at the end of the study, and was discharged after fifteen days in the hospital.

Period I lasted for 3.7 days, from midnight on September 14, until 3:00 P.M. on September 18. By intravenous drip he received the following: First day, lactate—potassium chloride—sodium chloride mixture, 625 Gm.; 5 per cent glucose, 390 Gm.; blood 60 c.c.; plasma 50 c.c. Second day, lactate—potassium chloride—sodium chloride mixture, 587 Gm.; 5 per cent glucose, 557 grams; blood 50 c.c. Third day, lactate—potassium chloride—sodium chloride mixture, 577 Gm.; and 5 per cent glucose, 330 Gm. Fourth day, lactate—potassium chloride—sodium chloride mixture, 506 Gm.; 5 per cent glucose, 348 c.c. Nothing was given by mouth except the last glucose. On the successive days the stools weighed 340, 436, 455, and 151 Gm., respectively. The body weight changed from 5,950 to 6,650 Gm.

Period II lasted for 3 days, from 3:00 P.M. on September 18, until 3:00 P.M. on September 21. The milk mixtures were all made up to 800 c.c. with water and contained 20 calories per kilogram on the first day and 60 on the last two days. About 50 Gm. of stool were lost at the beginning of this period. The final weight of the stools of this period was considered to be 50 Gm. greater than the amount collected. This correction is about 5 per cent of the whole, so it is felt that the lost stool does not make a significant error for the period as a whole. The body weight changed from 6,650 to 6,550 Gm.

Period III lasted for 3.87 days, from 3:00 P.M. on September 21, until noon on September 25. The baby was fed a volume of 800 c.c. with calories at about 90 per kilogram. The weight changed from 6,550 to 7,060 Gm.

TABLE VI. BALANCE IN CASE 6

	SOLIDS Gm.	H_2O Gm.	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	BODY WEIGHT Kg.
				Period I (3.5 Days)					
Intake	75	3,874	0.0	348	428	119.1	0.0	0.0	5.95
Urine		1,149	5.22	50	64	51.8	16.1		
Stools	43	1,387	3.83	152	154	10.8	10.6	1.12	
Balance			–9.05	146	210	56.5	–26.7	–1.12	6.65
				Period II (3 Days)					
Intake	281	1,889	4.47	35	26	36.3	33.9	33.9	
Urine		1,110	2.41	5	20	6.7	4.9		
Stools	44	486	1.66	19	58	30.0	22.9	30.4	
Balance			0.40	11	–52	–0.4	6.1	3.5	6.55
				Period III (3.87 Days)					
Intake	750	2,530	15.83	97	78	131.5	95.2	88.0	
Urine		590	5.25	45	11	3.5	17.3		
Stools	65	670	2.20	6	20	61.2	52.0	83.5	
Balance			8.38	46	47	66.8	25.9	4.5	7.06

SALIENT FINDINGS OF THE BALANCES

The data show that water, chloride, sodium, and potassium were retained in all cases during recovery from diarrhea. These retentions give a measure of the probable deficits produced by diarrhea. Since the findings vary somewhat in the different patients, attention will be directed to certain facts in each case.

In Case 1, the patient suffered from rather marked acidosis (serum bicarbonate 5.8 mM per liter) due to diarrhea of short duration. Recovery was rapid with no diarrhea in the hospital. During Period I, when he was treated with solutions containing sodium and chloride, 67 mM of sodium and 13 mM of chloride were retained. Serum bicarbonate was normal after the first day. It is surprising, therefore, to find most of the retained sodium was excreted during Period II, while more chloride was retained. Even in Period III, more chloride

TABLE VII. CONCENTRATION PER LITER OF SERUM

CASE	DATE 1945	H_2O Gm.	HCO_3 mM	Cl mM	Na mM	K mM	pH
1	1-18	920	5.8	100	130	7.4	
1	1-19	943	20.8	104	135	4.6	
1	1-20	951	25.0	95	138	4.9	7.38
1	1-22	948	27.2	102	140	6.8	7.35
1	1-25	942	27.6	86	134	5.8	7.40
2	4-18	926	10.2	103	128	6.7	7.08
2	4-20	944	21.6	92	137	5.0	7.49
2	4-23	945	23.7	98	131	6.8	7.51
2	4-27	940	25.0	95	137	7.9	7.40
3	8-20	924	14.6	110	135	5.0	
3	8-22	934	25.5	95	130	3.5	
3	8-25	937	19.2	109	136	5.4	
4	8-21	917	18.3	100	135	5.5	
4	8-23	934	27.3	100	135	3.4	
4	8-27	933	23.3	97	139	4.9	
4	8-30	934	23.0	110	141	4.5	
5	9-4	923	6.7	121	138	4.8	
5	9-8	942	20.5	116	145	4.8	
5	9-13	948	24.3	110	139	6.3	
5	9-17	939	22.2	108	135	6.3	
6	9-14	925	16.6	95	131	3.7	
6	9-18	951	36.4	94	138	4.8	
6	9-21	940	27.5	102	136	4.7	
6	9-25	935	24.4	104	133	4.9	

than sodium was retained. Such balances could not have occurred without acidosis again developing if both sodium and chloride had remained extracellular. The probable course of events is illustrated in Chart 1. Here a little more than one-half of the sodium balance of Period I is shown to have been contained in the intracellular fluids. In the second period there is a reduction of intracellular sodium below the level at the beginning of the study. Loss of intracellular sodium continued during the third period. It will be noticed that the total net loss of intracellular sodium is about two times greater than the estimated normal content. As would be expected from the lack of intake of potassium, there is a negative balance of this cation during Period I. In the chart the loss of potassium is shown to be somewhat greater than would be explained by the negative balance of nitrogen. In Periods II and III, potassium not accounted for by nitrogen storage was retained in amounts equivalent to about 10 per cent of the estimated normal content.

The patient apparently had a moderate deficit of potassium on admission and had transferred a considerable amount of sodium to the intracellular fluids. The initial low concentration of serum bicarbonate is explained chiefly by loss of sodium from extracellular fluids through transfer of sodium to the intracellular fluids, rather than by true deficit of body sodium. Since the transfer was probably connected with the deficit of potassium, the acidosis of the serum was in part due to loss of body potassium. In this case the changes in intracellular phosphorus are negligible. This case is of particular importance, for it demonstrates that treatment of certain types of acidosis with sodium bicarbonate will restore serum concentrations of bicarbonate, but aggravate the disturbance

in intracellular fluids. The disturbance in the cells is a deficit of potassium and excessive retention of sodium, and these changes cannot be corrected until potassium is available.

In Case 2, the patient suffered from a fairly severe acidosis due to diarrhea. Recovery was somewhat slow in this case. The initial serum showed both low bicarbonate and sodium concentrations (respectively, 10 and 128 mM per liter).

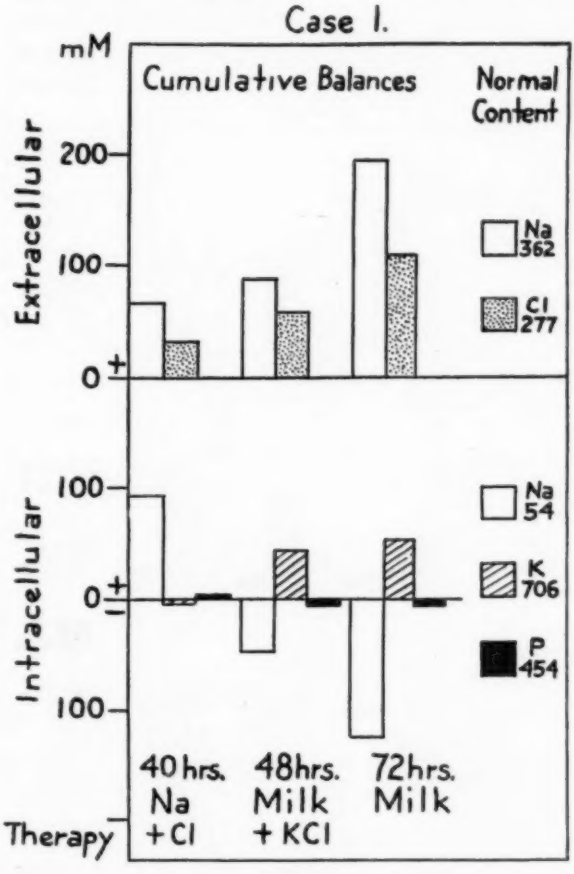

Chart 1.

Subsequently serum electrolyte was approximately normal except for slightly low chloride at the end of Period I, and slightly low sodium at the end of Period II. Correction of the extracellular acidosis is accounted for by the retention of 102 mM of sodium and 55 mM of chloride in Period I. Chart 2 shows that most of the sodium and chloride remained extracellular in Period I. Subsequently both sodium and chloride were excreted in approximately equivalent amounts, but an amount of sodium became intracellular which is about equal to the nor-

mal estimated intracellular content. During the fasting, when no potassium was given, some intracellular potassium was excreted in excess of that accounted for by nitrogen loss. During the last two periods potassium was retained equal to about 14 per cent of the estimated normal content. The changes in intracellular phosphorus are negligible in this patient.

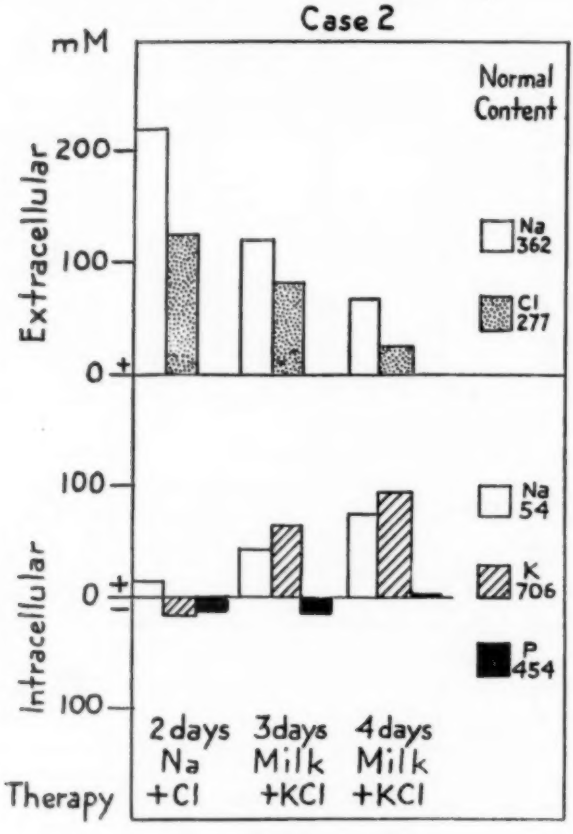

Chart 2.

On admission the acidosis is explained by a deficit of sodium in both intracellular and extracellular fluids. In addition to a deficit of sodium, the intracellular fluids had a considerable deficit of potassium.

In Case 3, the patient suffered from a fairly severe attack of diarrhea which responded somewhat slowly to treatment. The lack of rapid recovery in this case was probably in part due to an attempt to start feeding a little too early. On admission there was only moderate reduction in the concentration of serum bicarbonate (14 mM per liter), essentially normal serum sodium, and high serum chloride (110 mM per liter). Subsequent serum concentrations were

approximately normal except for the slight reduction in serum sodium and chloride at the end of Period I. During fasting and administration of sodium chloride, sodium lactate, and glucose (Period I), about twice as much sodium (93 mM) as chloride (41 mM) was retained. A moderate amount of this sodium became intracellular (Chart 3). During the second period enough sodium was excreted while chloride was retained, to make the final retention of chloride greater than that of sodium (101 mM as contrasted to 35 mM). Chart 3 illustrates that the sodium lost from the cells is about twice the estimated normal content. During the first period, potassium was lost from the cells, but enough

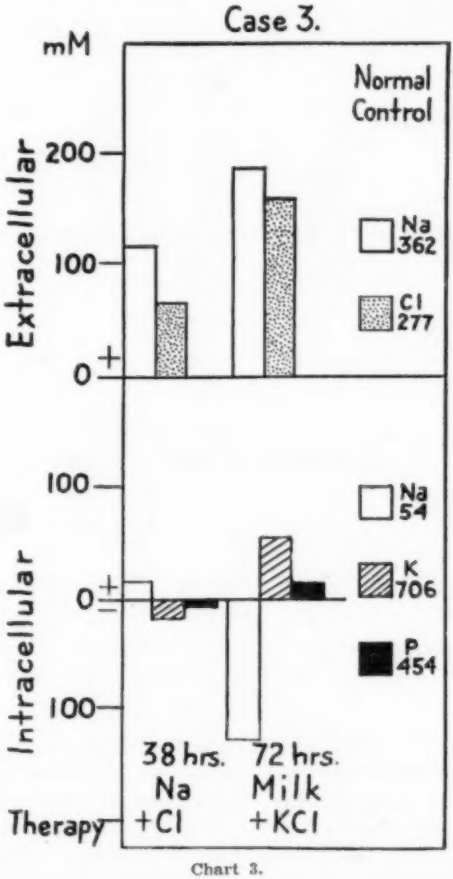

Chart 3.

was retained in the second period to make the final retention of potassium equal to about 11 per cent of the estimated normal content. Appreciable retention of intracellular phosphorus occurred in this patient.

The state of body fluids on admission was much the same in Cases 1 and 3; that is, there was excessive intracellular sodium and a deficit of potassium.

In Case 4, the patient suffered from a severe attack of diarrhea and vomiting which responded slowly to treatment. This patient also was probably fed too soon. On admission, the serum bicarbonate was only slightly reduced; subsequent serum concentrations were approximately normal. During the fasting

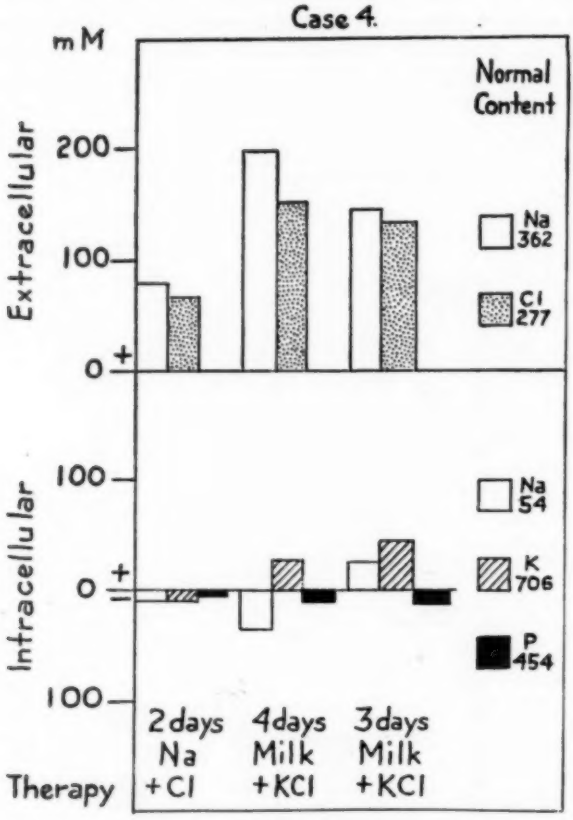

Chart 4.

and administration of sodium chloride, sodium lactate and glucose, the retention of sodium was 85 and chloride, 75 mM. In the second period considerable sodium and chloride were retained. In the last period small amounts of these ions were lost. Chart 4 shows rather small shifts of sodium into and out of the intracellular fluids. Relative to size, this patient retained less potassium than any of the other patients. There was no significant change in intracellular phosphorus in relation to nitrogen.

On admission this patient apparently suffered chiefly from loss of extracellular sodium and chloride, though there was a loss of about 7 per cent of the estimated normal content of potassium. This patient never received adequate calories during the study because his appetite remained poor. This fact and

the apparent lack of satisfactory recovery during the study suggest that a period on adequate calories might have revealed a greater deficit of potassium in this patient. This surmise, however, is not supported by the finding of a relatively high concentration of potassium in the urine of Periods II and III.

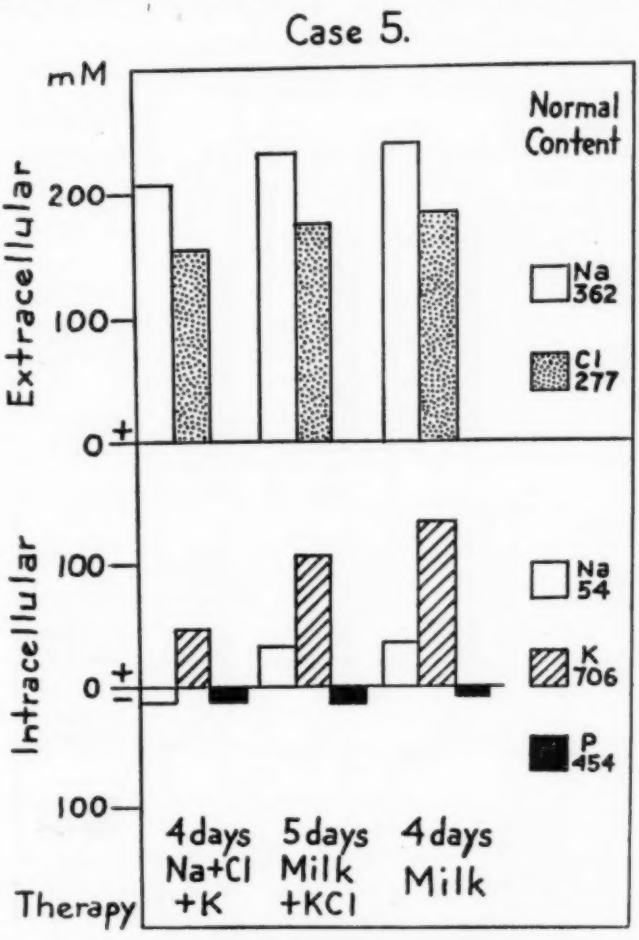

Chart 5.

In Case 5, the patient had suffered for eight days from fever and severe diarrhea and vomiting. He had marked signs of dehydration, acidosis, and shock. Recovery seemed unlikely for three days. While his diarrhea and gastro-intestinal disturbances were improved at the end of the study, he required twenty-three days in the hospital to assure proper convalescence.

During Period I, this patient received daily intravenous injections of potassium chloride as well as sodium chloride, sodium lactate, glucose, and blood.

This treatment led to the retention of 106 mM of sodium, 85 mM of chloride, and 15 mM of potassium. These retentions explain the rise in serum bicarbonate from 7 to 21 mM per liter. On admission, serum chloride was 121 mM per liter and it remained high during the entire duration of the study. When food fortified with potassium chloride was given in Period II, a large amount of

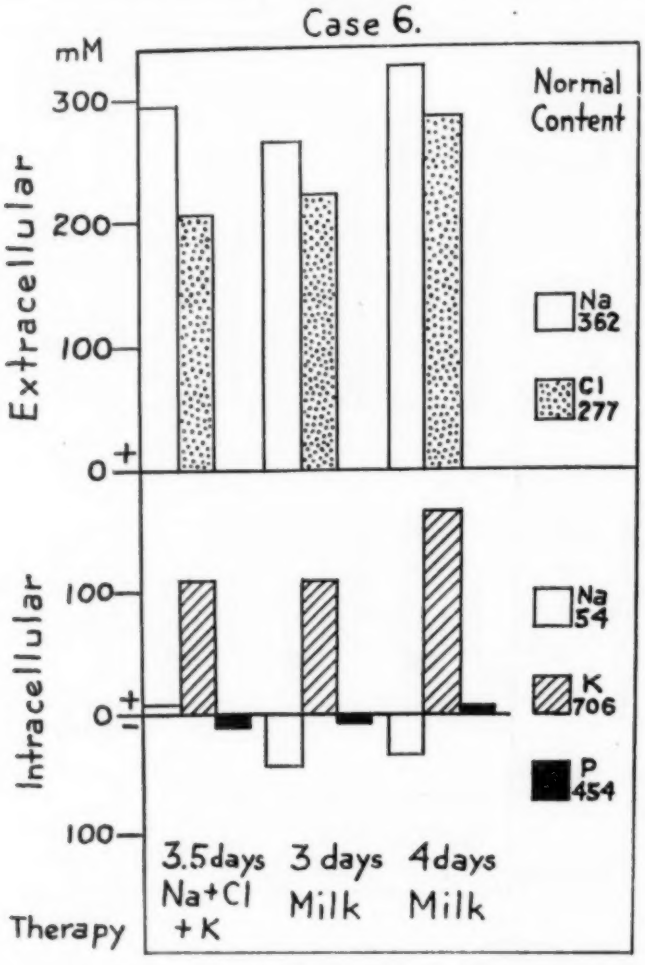

Chart 6.

potassium was retained, together with a considerable amount of sodium and a small amount of chloride. The last period shows chiefly retention of potassium. Chart 5 shows that the sodium and chloride were chiefly retained in the extracellular fluids. The final retention of potassium is equal to about 19 per cent of the estimated normal content. The changes in intracellular phosphorus are negligible.

On admission, the state of body fluids and electrolyte of Case 5 differed from the previous ones chiefly in the magnitude of the deficit of potassium. While there may have been a slight loss of intracellular sodium, no change in intracellular phosphorus was demonstrated.

In Case 6, the patient suffered from severe bacillary dysentery of four days' duration. This patient showed extreme dehydration and fairly marked evidences of shock. As shown in the protocol, he had daily stool volumes equal to almost 8 per cent of the body weight during Period I. Recovery was satisfactory at the end of the study.

During the period of fasting the patient received daily intravenous injections of potassium chloride as well as sodium chloride, sodium lactate, glucose, and blood. When food was started in Period II, no potassium chloride was added to the milk mixture. In Period I, large amounts of potassium, sodium, and chloride were retained. If one takes into account the loss of about 27 mM of potassium which would usually accompany a negative balance of 9 Gm. of nitrogen, the retention of 57 mM of potassium in Period I is quite remarkable. The lack of retention of potassium in Period II is dependent on the increase in stool potassium. Since potassium was retained in Period III, it would probably have also been retained in Period II, if potassium chloride had been added to the food. It is this finding in Case 6 which indicates that 1 to 2 Gm. of potassium chloride should be added to a day's feeding when less than 70 calories per kilogram are taken. On the other hand, the findings in Period III indicate that, when adequate calories can be tolerated, sufficient potassium will be obtained from the usual milk mixtures.

The final retention of potassium in this case is equal to about 23 per cent of the estimated normal content. The changes in intracellular phosphorus are negligible and the loss of intracellular sodium is about two-thirds of estimated normal intracellular content. On admission to the hospital the change in body electrolyte was a deficit of intracellular potassium and sodium, and a deficit of extracellular sodium and chloride.

DISCUSSION

In the presentation of the data, emphasis was placed on the relation of the balance of nitrogen to the retentions of sodium, chloride, phosphorus, and potassium. There was in each case a deficit of extracellular sodium and chloride which cannot be exactly assayed for reasons that will be mentioned later. Previously, the balances of sodium and potassium have been correlated with the balance of water. The latter system tends to measure the balances of water in terms of some assumed relation of electrolyte concentration to water within the cells. The system used in this paper makes the tacit assumption that if the retentions of phosphorus, potassium, and nitrogen enable the cells to have a normal relationship of these constituents to each other, the correct amount of water will be retained to reconstitute normal cytoplasm. Inspection of the data shows that in every case, but particularly in Cases 5 and 6, the retentions of sodium and potassium are so great that they would lead to high concentration of sodium in the serum if a large part of the intracellular base were not relatively less dissociated than extracellular sodium. This finding confirms previous evi-

dences of variations in the activity of intracellular electrolyte.[1, 15] The magnitude of this sort of change cannot be measured without more accurate knowledge of body water than the present data give. To correlate the retentions of univalent cations with the changes in body water, assurance of a normal state of body tissues at the beginning or end of a balance study is probably necessary.

In the calculations of the shift of sodium across the cell membranes, the change in extracellular volume is calculated from an assumed volume of extracellular water, the balance of chloride, and the serum chloride concentrations. Within the probable values, the assumed initial volume of extracellular water does not make very much difference in the calculated shift of sodium if the balances of sodium and chloride are large. However, the relative change in volume of extracellular water depends on the initial volume of extracellular water and hence such calculations require an accurate measurement of the extracellular volume in order to have validity for predicting intracellular changes in concentration.

The data of this paper do not show directly which tissues account for the deficit of potassium. However, such large deficits as were demonstrated must involve the muscle, since no other tissue has sufficient mass to account for the changes. The importance of changes in muscle composition is substantiated by experimental work which shows that the liver does not undergo loss of potassium in animals receiving diets low in potassium or injections of desoxycorticosterone acetate.[4, 7] Similar animals showed low potassium in the heart[4, 5] and the brain.[16] In the demonstrated shifts of sodium, muscle also plays the leading role, since substitution of sodium for potassium has been demonstrated only in muscle and heart tissue.[4] The liver loses potassium and gains sodium in shock,[17] but this is probably not the same type of change as has been described in a deficit of potassium in muscle. Whatever changes are taking place in other tissues, skeletal muscle accounts for a large part of the loss of potassium and most of the evidences of shift of sodium into and out of the intracellular fluids.

Although Tobler's[18] analyses of muscle in babies dying of diarrhea do not agree in absolute values with modern analyses, they indicate a reduction of 30 per cent of the potassium. The author has analyzed several samples of muscle from babies dying of diarrhea, some of the samples showed a decrease in potassium in relation to fat-free solids equal to about 40 per cent of the normal content. Some of the tissues showed high intracellular sodium, but most of the samples did not. Loss of 40 per cent of the muscle potassium is sufficient to account for the deficits demonstrated in Cases 5 and 6.

The tissue analyses of babies dying of diarrhea showed decreases in muscle phosphorus in some cases equal to 20 per cent of the normal content and usually equal to 10 per cent. It is surprising, therefore, to find that the metabolism studies did not show retentions of intracellular phosphorus during recovery. The phosphorus deficits found in the autopsy material may represent a late stage in the depletion of intracellular electrolyte. Guest and Rapoport[19] reported changes in phosphorus compounds in the red cells in acidosis and advised the use of phosphate in the treatment of acidosis. While the metabolic data do not demonstrate that a deficit of phosphorus is of great importance in diarrhea,

further study may show that therapy directed toward minimizing the loss of phosphorus is indicated.

The charts show rather large retentions of sodium and chloride at the end of the balance periods, in all cases except Case 2. Experimental work[20] on cats and dogs showed that the clinical picture of marked dehydration was produced when about one-third of the extracellular electrolyte was removed, and that loss of about one-half of the extracellular electrolyte was as much as an animal could survive. The retention of sodium was more than one-half the estimated content in Cases 5 and 6 and about one-half in Cases 1 and 3. Overexpansion of the extracellular fluids was almost certainly produced in Cases 5 and 6, and probably in Cases 1 and 3. In none of the cases did pitting edema appear, but puffiness about the eyes developed transiently in all but Case 2. Because of the tendency to retention of sodium chloride, the present technique would be difficult to use to demonstrate the actual magnitude of the deficits of extracellular sodium and chloride on admission. From a therapeutic point of view, moderate overexpansion of extracelluar fluids is probably harmless and is certainly less dangerous than under-replacement of sodium and chloride.

The data are striking in that they demonstrate that the loss of nitrogen is rapidly restored. During the fasting (Period I), relatively large amounts of nitrogen were excreted, particularly in Case 6; loss of nonprotein nitrogen may account for part of this loss. The rate of excretion of nitrogen diminished markedly in the second period when submaintenance feedings were given. With the exception of Case 4, in which maintenance calories were not taken during the study, in all cases the deficit of nitrogen developing during treatment was restored by the end of the period of observation. This finding is surprising because a positive balance appears almost as soon as milk is given even at a low calorie intake (particularly Cases 1 and 3). While it might be argued that more rapid recovery would be produced by intravenous injection of amino acids, restoration of nitrogen is quite rapid as soon as food is taken. On the other hand, the data do not show how great a deficit of nitrogen had developed before the patients entered the hospital. The data suggest that the importance of such a deficit should be demonstrated before one is justified in administering amino acids intravenously, if this procedure is to interfere with replacement of water and electrolyte. Such will be the case if thrombosis or febrile reactions are produced by injection of amino acids.

From the point of view of therapy, the present study emphasizes the losses of nitrogen, sodium, chloride, and potassium. However, it is chiefly the loss of potassium that takes on new significance since its magnitude is brought into view and the possibility of restoration without food is demonstrated.

Actually the demonstration of the loss of potassium as well as sodium and chloride in diarrhea is not new. In 1850, Schmidt[21] showed that loss of water, sodium, chloride, and potassium occurred in cholera and dysentery. His terminology and grasp of the problem were so sound that it is surprising that his work was not followed by the development of modern concepts of the physiology of water and electrolyte. Steinitz[22] demonstrated that the acidosis of diarrhea was due to loss of more fixed base than acid. Meyer[23] showed that a baby developing rapid decrease in body weight owing to diarrhea lost considerable amounts of

sodium and potassium. His data show that the loss of potassium is greater than can be accounted for by the loss of nitrogen. Tobler[18] showed that the muscle of babies dying of diarrhea had low concentrations of potassium. By analysis of the tissues of puppies dying following experimental diarrhea, Tobler[24] showed that most of the water loss was sustained by subcutaneous tissues and muscle. These tissues accounted for most of the loss of sodium and potassium. The losses of electrolyte were roughly proportional to the losses of water—chloride and potassium showing the closest parallelism. Nitrogen was not lost as rapidly proportionately as water, sodium, chloride, and potassium. Tobler appreciated that the tissues were not breaking down as a unit, but thought that the losses of potassium and water indicated a fundamental disintegration of the cells. Jundell,[25] while working in Finkelstein's clinic, determined the balances in mild and severe diarrhea. He related the losses of sodium, chloride, potassium, and nitrogen to each other and to the composition of muscle. He realized that potassium was being lost at a greater relative rate than nitrogen, but thought this was probably due to failure of the kidneys to eliminate nitrogen. The losses of potassium in his patients were not as great as in Meyer's[23] patient or in Cases 5 and 6. Meyer's study illustrates the reversal of the losses while recovery occurred in a baby receiving human milk. If emphasis had been placed on the fact that the retention of potassium preceded the retention of sodium and chloride, other studies would doubtless have been made to evaluate this observation and deduce its therapeutic significance.

Thus the great school of pediatrics in Germany which culminated under the leadership of Czerny and Finkelstein appreciated that loss of alkali was an essential feature of malignant diarrhea and that potassium was lost in relative excess of nitrogen. They conceived of the rapid terminal loss of nitrogen as a consequence of the loss of alkali. In this assumption they may have been correct, but they were not correct in assuming that the process could not be reversed by specific replacement therapy.

Holt, Courtney, and Fales[26] showed that the loss of potassium in diarrheal stools is greater than can be accounted for by the loss of nitrogen. That Holt appreciated the implications of these findings is indicated by the following quotation: "In attempting to supply this loss by hypodermoclysis it should be remembered that not only are water and sodium needed, but potassium and magnesium as well. With these facts in mind, a better solution for use in hypodermoclysis can certainly be devised than normal saline or than Ringer's solution." Holt, Jr.,[27] reported additional data obtained by his father and was impressed by the same findings, for he wrote: "A comparison of potassium and nitrogen retentions shows that loss of potassium is seldom accompanied by a proportionate loss of nitrogen and may even be accompanied by a retention of nitrogen. The conclusion to be drawn from this is that intracellular fluid may be lost without death of the cells. Hitherto, attention has been directed only to the replacement of plasma electrolyte and that of interstitial tissue fluid. The question of replacing intracellular fluids appears of equal importance and should by no means be neglected."

Butler, McKhann, and Gamble[28] reported data essentially like those of the present paper except for omission of chloride balances. Again a quotation in-

dicates appreciation of the significance of the findings: "The presence of an intracellular fluid loss complicates our conception of the process of dehydration and disturbs our confidence in the therapeutic adequacy of parenteral treatment. Since repair solutions must be placed in the vascular or in the interstitial compartment, they cannot contain with safety the intracellular materials, such as potassium and phosphate, at concentrations above the small values prescribed for them in extracelluar fluids. The solution devised by Hartmann contains potassium appropriately to this extent. It is evident, however, that such solutions cannot provide an adequate replenishment of intracellular materials. Parenteral therapy has a large, often dramatic, effectiveness. It must be admitted, however, that it is not always successful and it may be hoped that recognition of an additional pathologic process in the situation will eventually produce supplementary measures which will provide a more complete control of the severe stage of diarrheal disease."

These quotations raise the question of why adequate amounts of potassium were not given. The German students sought to treat diarrhea largely by providing some food which would change the character of the stools from diarrheal to "dyspeptic"; that is, from stools containing large amounts of sodium and potassium to ones containing little alkali and large amounts of calcium and magnesium soaps. In this they were partially successful as indicated by the survival of Finkelstein's protein milk. They appreciated that subcutaneous saline produced considerable improvement, but felt that if the stools remained watery a relapse into a worse state would occur. Because of this attitude the possibilities of replacement therapy were never adequately explored in Germany.

In this country, replacement therapy has been quite thoroughly tried, usually guided by chemical examination of the blood. In fact, restoration of normal plasma electrolyte has seemed so desirable that this end has been sought even though clinical signs and other evidences have indicated that normal serum concentrations do not restore the functions of a child who has suffered from dehydration due to diarrhea. The very success of some of the therapeutic procedures seems to have diverted pediatricians' attention from the importance of loss of potassium.

The use of large quantities of physiological saline by intraperitoneal injection produced a gratifying decrease in the mortality. While this route has been largely abandoned in favor of subcutaneous and intravenous therapy, Blackfan and Maxey's[29] work showed that diarrheal patients need large amounts of sodium chloride. The demonstration of serum acidosis by Howland and Marriott,[30] and Schloss and Stetson[31] was accompanied by proof that the acidosis could be corrected by the intravenous injection of sodium bicarbonate. However, the improvement in the symptoms of acidosis and the restoration of the concentration of blood bicarbonate seemed to both groups of workers to raise false hopes that were not fulfilled by a decrease in mortality. The original reaction to the use of sodium bicarbonate is confirmed by the high mortality of Hartmann's patients who were given large amounts of sodium lactate and in whom restoration of serum bicarbonate was used as a criterion of successful treatment.[41] Several papers[32-41] have shown the nature of the disturbances in serum concentrations

and made various recommendations for treatment. Powers[42] introduced the use of transfusions and correctly pointed out that the indication for transfusions is shock and only secondarily, anemia. He described a form of treatment which combined most of the contemporarily accepted procedures. The outline emphasizes the use of fasting followed by small feedings, intraperitoneal injection of physiological saline, and intravenous glucose and blood transfusions. The mortality records of this series suggest that these procedures accomplished as much as any of the more recent modifications using constant intravenous injections and precisely calculated doses of sodium bicarbonate or sodium lactate.[41]

Ultimately, the failure to use potassium salts parenterally was apparently connected with two ideas. First, it was realized that a rise in the concentration of potassium in plasma could produce death by stopping the heart. Second, cellular membranes were considered to be relatively impermeable to cations and hence loss of potassium was considered to be caused by some fundamental change within the cells. As indicated in the introduction, the second surmise is no longer tenable and recent studies have shown that the dangers of potassium poisoning, although real, are not as great as might be anticipated.

Heart block is produced when the serum concentration of potassium reaches a level of 10 to 12 mM per liter.[43] The disturbance in the heart is connected with the rise in extracellular concentration and not directly associated with a rise in the intracellular potassium of the heart.[44] In the parenteral injection of potassium salts, the rate of administration must be slow enough not to lead to a temporary rise to toxic levels and the total dose must not be large enough to lead eventually to a toxic extracellular concentration.

When potassium chloride is injected intravenously, the serum concentration increases as if potassium were distributed equally throughout body water.[45] Actually it is known that the liver and heart take up relatively more potassium than other tissues when the serum concentration increases.[46] Temporarily the muscle content can increase 5 to 8 per cent above the high normal level.[6] Since the intracellular water of the muscle makes up about 70 per cent of the total intracellular water, such an increase can amount to about 4 mM of potassium per kilogram of body weight and about one-half of this rise may occur before the serum concentration reaches 10 mM per liter. The kidneys are capable of excreting potassium in a concentration of over 100 mM per liter so that a dangerous rise in potassium concentration is unlikely to develop as long as urine is being excreted. During the period of fasting, the first four cases showed urine concentrations of potassium varying from 11 to 30 mM per liter and excreted 2 to 5 mM of potassium per day in the urine. In Cases 5 and 6, the concentrations were 68 and 45 mM potassium per liter, and the daily urinary excretion 8.5 and 6 mM, respectively. Thus the parenteral potassium did not produce unusual urinary concentrations. The transfer of potassium to the cells explains this finding. Miller and Darrow[6] showed that the toxic dose of potassium chloride injected into the peritoneal cavity is about twice as large in rats with a deficit of muscle potassium as in normal rats. The resistance to potassium poisoning was explained by a rise in muscle potassium accompanying injections of potassium chloride.

Bearing these facts in mind, one can predict with reasonable certainty the safe dose of potassium for intravenous or subcutaneous use. If the concentra-

tion of serum potassium is 5 mM per liter, a rise in concentration of 4.5 mM will not produce heart block. Assuming equal distribution throughout body water, 3.1 mM of potassium per kilogram of body weight will produce a rise of 4.5 mM in the concentration of serum potassium. If injected slowly, this amount of potassium should be safe for the treatment of diarrhea unless the serum concentration is already high and urine is not being formed. Injection over a period of four to eight hours should assure equal distribution of injected potassium and avoid a sudden rise in the serum concentration.

In the practical choice of a solution for parenteral use, the safe dose of potassium was added to quantities of sodium chloride and sodium lactate suitable for replacing extracellular electrolyte. Darrow and Yannet[1, 20] showed that from one-third to one-half of the extracellular electrolyte must be removed to produce the picture of advanced dehydration. This amount of electrolyte is contained in 80 to 100 c.c. of physiological saline per kilogram of body weight. Since a greater amount of sodium than chloride is desirable, sodium lactate was included. The concentrations used in this study were approximately: potassium chloride, 40; sodium chloride, 100; and sodium lactate, 50 mM per liter. Such a solution can be made by adding 40 c.c. molar sodium lactate, 2 Gm. potassium chloride, and 3 Gm. sodium chloride to 710 c.c. of water. The sodium chloride and potassium chloride can be sterilized separately and added, together with one 40 c.c. ampule of molar sodium lactate, to 710 c.c. of sterile water. This solution is not irritating when given subcutaneously and will not produce potassium intoxication in the recommended doses given over a period of four to eight hours.

Untreated patients suffering from the dehydration of diarrhea may have a high concentration of potassium in the serum. In Case 6, the serum concentration was slightly low (3.7 mM per liter) while in the other cases the potassium concentration was slightly high on admission (4.8 to 6.7 mM per liter). However, the author has found levels as high as 10 to 12 mM per liter in moribund diarrheal patients. This finding suggests that the poor circulation of the terminal stages tends to lead to loss of potassium from the cells, in spite of a deficit of potassium in intracellular fluids. This finding is in agreement with recent data on shock produced by tourniquets.[53] Hence in moribund patients and perhaps in all cases of severe diarrhea, infusions of physiological saline and glucose solutions should be initiated for an hour or until urine formation is assured, and then the solution containing potassium chloride can be started.

In Cases 5 and 6, and in the series reported elsewhere,[51] treatment was carried out with the solution containing potassium chloride as well as sodium chloride and sodium lactate. In severe dehydration, the initial deficit of sodium and chloride should be replaced by 80 to 100 c.c. of such a solution, and at the same time potassium will be given at a safe rate. The solution will have to be injected repeatedly as long as the diarrhea continues and parenteral fluids are given. When submaintenance feeding is started, retention of potassium will be promoted if 1 to 2 Gm. of potassium chloride are added to the food each day. When maintenance feeding can be taken without inducing watery stools, no potassium chloride need be added to the food.

The present work shows that failure to give potassium is a factor in the untoward results obtained previously. The reduction in concentration of serum potassium is probably one of the untoward effects of the usual therapy. Considering 4 mM per liter the low normal level of potassium in serum, the cases illustrate this difficulty. At the end of Period I, the serum potassium concentration was below 4 mM per liter in Cases 3 and 4, but not in Cases 1, 2, 5, and 6. In Case 1, there was no diarrhea in the hospital and in Cases 5 and 6, potassium was given in Period I. Increase in intracellular sodium may be a second untoward effect of the usual replacement therapy. In Case 1, considerable sodium entered the cells and explains why a large retention of sodium and a small retention of chloride raised the serum bicarbonate no higher than normal. Elsewhere[13] the bearing of a deficit of the intracellular sodium on the dose of sodium bicarbonate necessary to restore the serum bicarbonate in acidosis is discussed. It is obvious that the dose of sodium bicarbonate might be quite enormous if sodium is transferred to the intracellular fluids to replace all of a large deficit of potassium in the cells. The present data show that the deficit of potassium may be equivalent to one-half of the estimated extracellular sodium of the body (or one-quarter of the estimated potassium of the body) and that substitution of sodium for the deficit of potassium is likely if bicarbonate therapy is pushed. If a high intracellular sodium concentration is harmful, aggravation of this type of change in the cells is undesirable. More research into the consequences of this phenomenon must be made before its role in the untoward effect of therapy with sodium chloride and sodium bicarbonate can be decided. It suffices here to state that the treatment of acidosis should not be undertaken without considering the effect on the cells; probably the use of the salts of both sodium and potassium is usually indicated in other types as well as in diarrheal acidosis.

Actually it is known that certain functions are affected by a deficit of potassium. Familial paralysis[47] is accompanied by a low concentration of serum potassium and similar paralysis has been observed in dogs having low serum potassium as a result of injections of desoxycorticosterone acetate.[7] It is unlikely that this type of reaction develops in untreated diarrheal patients, since untreated cases are apt to have high serum potassium concentrations. After treatment with sodium and chloride, such an occurrence is a possibility. Meyer and Nassau[48] emphasized that loss of muscle tone is an invariable accompaniment of severe diarrhea. Deficit of muscle potassium is probably associated with this phenomenon. Diets low in potassium and repeated injections of desoxycorticosterone acetate produce myocardial necrosis in experimental animals.[49, 5, 4] Myocardial failure is the usual sign of overdosage with desoxycorticosterone acetate.[50] One of the most ominous signs in diarrhea is a slow heart rate. Further study may show that the heart symptoms in diarrhea are dependent in part on a deficit of potassium. Thus, nervous, muscular, and cardiac disturbances can be produced by a deficit of potassium, but further study will be necessary to differentiate the disturbances associated with a deficit of potassium from those produced by a loss of sodium, chloride, and water.

Elsewhere[51] a modification of present methods of treating diarrhea is described. Although the only significant change is the parenteral administration

of potassium, the method lowered the mortality rate from 25 per cent to about 5 per cent. Harrison, Tompsett, and Barr[52] observed improvement in two adults suffering from fatty diarrhea when they were given potassium by mouth. These authors correctly concluded that the finding of a low concentration of potassium in serum indicated that potassium may be lost so rapidly in diarrheal stools as to lead to a deficit of body potassium and that this deficit can be reversed by giving potassium salts.

SUMMARY

Balances of nitrogen, sodium, chloride, potassium, phosphorus, and calcium are reported during recovery from dehydration due to severe diarrhea. The balances are correlated with each other to bring into view the disturbances in composition of the intracellular as well as the extracellular fluids.

Diarrhea led to a decrease in extracellular water owing to loss of sodium and chloride in extracellular fluid. In some cases, a large part of the loss of extracellular sodium was explained by transfer of sodium from the extracellular to the intracellular fluids. Such a transfer of sodium explained the acidosis in one case. In other cases, sodium was lost from the intracellular as well as extracellular fluids.

Loss of intracellular potassium was a prominent feature of all cases and was equivalent in two cases to about one-fourth of the estimated normal potassium content of the baby. This loss of potassium is in excess of the loss which would be expected from loss of nitrogen.

No great disturbance in the relative concentration of intracellular phosphorus was demonstrated.

The usual replacement therapy of fasting and the parenteral administration of solutions containing sodium chloride, sodium lactate, and glucose corrected the extracellular concentrations. However, considerable sodium entered the cells in two cases and loss of potassium was aggravated.

Replacement of intracellular potassium was obtained by adding 1 to 2 Gm. of potassium chloride to submaintenance feeding. One observation indicated that replacement of intracellular potassium is not likely to occur if the diarrhea continues and submaintenance milk feedings without added potassium chloride are given. The data indicate that the usual milk mixtures contain sufficient potassium to replenish the tissues if these mixtures can be taken in the amounts necessary for growth.

During the period of fasting, retention of intracellular potassium can be produced by adding potassium chloride to solutions containing sodium chloride and sodium lactate. Such a treatment restores extracellular concentrations and replaces the deficit of potassium in part. Accompanying this replenishment of both intracellular and extracellular electrolyte, the babies looked better than after the usual type of treatment and recovered from attacks of diarrhea that would usually be fatal.

The significance of a deficit of potassium is discussed.

REFERENCES

1. Yannet, H., and Darrow, D. C.: J. Biol. Chem. **134**: 721, 1940.
2. Darrow, D. C., Martins da Silva, M., and Stevenson, S. S.: J. PEDIAT. **27**: 43, 1945.
3. Heppel, L. A.: Am. J. Physiol. **127**: 385, 1939.
4. Darrow, D. C., and Miller, H. C.: J. Clin. Investigation **21**: 601, 1942.
5. Follis, R. H., Jr., Orent-Keiles, E., and McCollum, E. V.: Am. J. Path. **18**: 29, 1942.
6. Miller, H. C., and Darrow, D. C.: Am. J. Physiol. **130**: 747, 1940.
7. Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity, M. K., Atchley, D. W., and Loeb, R. F.: Am. J. Physiol. **135**: 230, 1941.
8. Miller, H. C.: Endocrinology **32**: 443, 1943.
9. Stewart, J. D., and Rourke, G. M.: J. Clin. Investigation **21**: 197, 1942.
10. Coller, F. A., Iob, V., Vaughan, H. H., Kalder, N. B., and Moyer, C. A.: Ann. Surg. **122**: 663, 1945.
11. McQuarrie, I., Johnson, R. M., and Ziegler, M. R.: Endocrinology **21**: 762, 1937.
12. Willson, D. M., Power, M. H., and Kepler, E. J.: J. Clin. Investigation **19**: 701, 1940.
13. Darrow, D. C.: New England J. Med. **233**: 91, 1945.
14. Darrow, D. C.: J. PEDIAT. **26**: 519, 1945.
15. Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: Yale J. Biol. & Med. **17**: 383, 1944.
16. Ziegler, M., Anderson, J. A., and McQuarrie, I.: Proc. Soc. Exper. Biol. & Med. **56**: 242, 1944.
17. Darrow, D. C., and Engel, F. L.: Am. J. Physiol. **145**: 32, 1945.
18. Tobler, L.: Arch. f. exper. Path. u. Pharmakol. **62**: 431, 1910.
19. Guest, G. M., and Rapoport, S.: Physiol. Rev. **21**: 410, 1941.
20. Darrow, D. C., and Yannet, H.: J. Clin. Investigation **14**: 266, 1935.
21. Schmidt, K.: Characteristik der epidemischen Cholera gegenüber verwandten Transudationsanomalien, G. A. Reyer's Verlagsbuchhandlung, Leipzig-Mitau, 1850.
22. Steinitz, F.: Jahrb. f. Kinderh. **57**: 689, 1903.
23. Meyer, L. F.: Jahrb. f. Kinderh. **71**: 379, 1910.
24. Tobler, L.: Jahrb. f. Kinderh. **73**: 566, 1911.
25. Jundell, I.: Ztschr. f. Kinderh. **8**: 235, 1913.
26. Holt, L. E., Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. **9**: 213, 1915.
27. Holt, L. E., Jr.: Am. J. Dis. Child. **39**: 1346, 1930.
28. Butler, A. N., McKhann, C. F., and Gamble, J. L.: J. PEDIAT. **3**: 84, 1933.
29. Blackfan, K. D., and Maxcy, K. F.: Am. J. Dis. Child. **15**: 19, 1918.
30. Howland, J., and Marriott, W. M.: Am. J. Dis. Child. **11**: 309, 1916.
31. Schloss, O. M., and Stetson, R. E.: Am. J. Dis. Child. **12**: 218, 1917.
32. Hamilton, B., Kajdi, L., and Meeker, D.: Am. J. Dis. Child. **38**: 314, 1929.
33. Hoag, L. A., and Marples, E.: Am. J. Dis. Child. **42**: 291, 1931.
34. Hartmann, A. F.: Am. J. Dis. Child. **35**: 557, 1928.
35. Smellie, J. M.: Lancet **1**: 969, 1026, 1939.
36. Marriott, W. M., Hartmann, A. F., and Senn, M. J.: J. PEDIAT. **3**: 181, 1933.
37. Karelitz, S., and Schick, B.: Am. J. Dis. Child. **42**: 781, 1931.
38. Schiff, E., Bayer, W., and Fukuyama, M.: Jahrb. f. Kinderh. **119**: 161, 1928.
39. Minot, A. S., and Dodd, K.: J. PEDIAT. **17**: 571, 1940.
40. Bridge, E. M., Cohen, M. I., and Scott, T. F. M.: J. PEDIAT. **18**: 709, 1941.
41. Hartmann, A. F., Perley, A. M., Basman, J., Nelson, M. V., and Asher, C.: J. PEDIAT. **13**: 692, 1938.
42. Powers, G. F.: Am. J. Dis. Child. **32**: 232, 1926.
43. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Am. J. Physiol. **124**: 478, 1938.
44. Crismon, J. M., Crismon, C. S., Calabresi, M., and Darrow, D. C.: Am. J. Physiol. **139**: 667, 1943.
45. Winkler, A. W., and Smith, P. K.: J. Biol. Chem. **124**: 589, 1938.
46. Noonan, T. R., Fenn, W. O., and Haege, L.: Am. J. Physiol. **132**: 474, 1941.
47. Talbot, J. H.: Medicine **20**: 85, 1941.
48. Meyer, L. F., and Nassau, E.: Die Säuglingsernährung. Eine Anleitung für Ärzte und Studierende, J. F. Borgmann, Munich.
49. Schrader, G. A., Prickett, C. O., and Salmon, W. D.: J. Nutrition **14**: 85, 1937.
50. McGavack, T. H.: J. Clin. Endocrinol. **1**: 68, 1941.
51. Govan, Clifton D., and Darrow, Daniel C.: J. PEDIAT. **28**: 541, 1946.
52. Harrison, H. E., Tompsett, R. R., and Barr, D. P.: Proc. Soc. Exper. Biol. & Med. **54**: 314, 1943.
53. Fox, C. L., and Keston, A. S.: Surg., Gynec. & Obst. **80**: 561, 1945.

THE USE OF POTASSIUM CHLORIDE IN THE TREATMENT OF THE DEHYDRATION OF DIARRHEA IN INFANTS

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THE comprehensive plan for the treatment of diarrhea published by Powers in 1926,[1] apparently produced as satisfactory results as any of the more recent systems. The later papers have advocated substitution of subcutaneous or intravenous injections of essentially the same solutions containing sodium chloride, sodium bicarbonate (or sodium lactate), and glucose in place of the intraperitoneal injections recommended by Powers. The dose of bicarbonate necessary to restore the concentration of serum bicarbonate has been more precisely defined.[2] However, the mortality records do not show that these refinements improve the final result. For all practical purposes no fundamental, new principle in the treatment of diarrhea has been introduced in the last twenty years.

In an accompanying report,[3] the magnitude of the loss of body potassium was shown to be equivalent to about one-quarter of the estimated body potassium in the most severe cases. Furthermore, it was demonstrated that this loss of potassium is not accounted for by disintegration of the cells as a whole; that is, the deficit of potassium was not accompanied by a corresponding loss of nitrogen and intracellular phosphorus. During the period of fasting, when all fluids were given parenterally, retention of potassium unaccompanied by a positive balance of nitrogen and intracellular phosphorus was produced by the addition of potassium chloride to the solutions in general use for the replacement of body water and electrolyte. These findings have formed the basis for the development of a new system of treatment which is described in the present paper. The results obtained by the new treatment are contrasted to the results obtained by the previous method.

The procedures used in the therapeutic trial cannot be precisely described. As in any type of treatment of diarrhea, the therapy varied a great deal as a result of varying severity of the symptoms, degree of dehydration, and the response of the diarrhea to treatment. In addition, the procedures used at the end of the study were the result of experience obtained earlier in the experimental trial. In other words, the system of treatment was a result of the information obtained with the new therapeutic agent during a therapeutic trial of its effectiveness. The following outline shows the general plan of treatment.

1. *Initial Treatment of Shock.*—On admission, in severe cases the patients received an intravenous injection of whole blood or plasma (10 to 20 c.c. per kilogram of body weight), together with an equal volume of physiological saline. This procedure sought to improve the circulation so that oliguria was

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overcome and a partial restoration of the functions of the enzyme systems of the cells would be obtained. Since it is not always possible to recognize the symptoms of shock* as distinguished from dehydration, transfusions were given in all severe cases before, rather than after, the development of obvious shock. In milder cases only saline and glucose intravenously were given for this purpose.

2. *Period of Fasting.*—Oral administration of food and water was withheld until all evidence of dehydration was overcome, nausea was no longer manifest, and intestinal functions had been partially restored. During this phase all fluids were given parenterally by slow intravenous injection, supplemented by subcutaneous injections in many cases. Nothing was given orally to any infant during the first twenty-four hours and a few infants received nothing by mouth for six days.

3. *Replacement of Body Water and Electrolyte.*—During the first twenty-four hours replacement of most of the deficit of body water and electrolyte was attempted by the subcutaneous or intravenous injection of from 80 to 150 c.c. per kilogram of body weight of a mixture of potassium chloride, sodium chloride, and sodium lactate (this mixture will be called potassium chloride-sodium chloride-lactate mixture and is described later). The rate of injection varied; it was given as rapidly as 2 c.c. per minute over a period of four hours; usually the estimated dose was given in from eight to twelve hours by slow drip. During this initial period of electrolyte replacement, enough 5 per cent solution of glucose was injected intravenously to make the total water intake from 150 to 280 c.c. per kilogram of body weight.

4. *Maintenance of Body Water and Electrolyte.*—After the first day, smaller amounts of the potassium chloride-sodium chloride-lactate mixture (from 20 to 50 c.c. per kilogram of body weight) were given daily as long as the stools remained watery. In addition, sufficient 5 per cent solution of glucose was injected intravenously to make the total fluid intake from 150 to 200 c.c. per kilogram of body weight. In some cases these glucose and electrolyte solutions were injected subcutaneously in a mixture of one-half potassium chloride-sodium chloride-lactate solution and one-half 5 per cent glucose.

In a few cases, a mixture of amino acids (Mead Johnson and Company) was added to the other fluids without obvious changes in the course as compared with those receiving no amino acids.

5. *Vitamins.*—Upjohn's Solu-B was added to the glucose solutions in the majority of cases. All patients were given intramuscularly 1 c.c. injections of crude liver extract twice a week.

*It is realized that the term shock is unsatisfactory since it has been applied to a number of conditions not clearly related to each other. In this paper the authors refer to evidences of permanent damage to the functions of the cells which develop as a result of diarrhea. Dehydration or deficit of body water and electrolyte does not mean the same thing, although eventually it leads to shock in this sense of the word. When the circulation is reduced for a sufficient period, secondary changes take place within the cells probably owing to anoxia. These are made manifest in the liver by failure of certain enzymes[4] and in the muscle by changes in the distribution of electrolyte.[5] It is probably failure of these cellular functions, rather than failure of the circulation, which explains the so-called irreversible stage of shock. At present, improvement of the circulation has been the most effective means of preventing and, to a certain extent, reversing the changes in cellular functions. In shock due to electrolyte deficit, restoration of body electrolyte is an essential part of the treatment, but plasma or blood makes electrolyte therapy appreciably more effective.

6. *Feeding.*—Food was started when the stools were no longer watery and all evidence of dehydration had been overcome. The period of fasting varied from one to six days. The food was milk with 2 per cent fat and 5 per cent dextrimaltose. The milk was made from powdered whole lactic milk and powdered skimmed milk restored to their original concentrations with water. Equal parts of these two reconstituted milks formed the basis of the food. During the first day after resumption of feeding, 10 calories per kilogram of body weight were offered. In most of the cases, the food was diluted with sufficient water to give 150 c.c. of fluid per kilogram of body weight per day. If the infant failed to take this amount of food, the fluid intake was supplemented by subcutaneous or intravenous injections of physiological saline or 5 per cent glucose. The feedings were increased gradually over a period of from seven to fourteen days until full feedings were taken.

Beginning in October, from 1 to 2 Gm. potassium chloride were added to each day's feeding when the caloric intake was less than 70 per kilogram of body weight.

Before instituting this treatment, essentially the same procedures had been carried out except (1) only physiological saline or a mixture of about two parts physiological saline with one part isotonic sodium lactate was used, and (2) no liver extract was used. One of the authors (D. C. D.) has used liver extract for years, but had never observed a definite beneficial result such as will be demonstrated when the series treated with potassium chloride-sodium chloride-lactate mixture is contrasted to the series receiving no parenteral potassium.

When the first patients received potassium intravenously, the clinical response was so striking that it was decided that it was important to obtain as wide an experience with the therapy as possible. For this reason all patients suffering from diarrhea received some form of potassium therapy after September. Hence there are no control cases coming at the same time of the year. However, from June to September about the same number of cases had been treated by the conventional therapy as were treated by the new method from September to November.

All the patients treated for diarrhea were babies brought to the Harriet Lane Home because of a chief complaint of diarrhea. All patients were seen and their treatment carried out under the direction of one of the authors (C. D. G.). Owing to limitation of the number of beds, only severely ill infants were admitted to the wards. As a result, the patients studied were only those infants who were thought unlikely to recover unless treated in the hospital. The clinical impression was that both groups were roughly comparable in degree of severity of the illness. The ages of the two groups were essentially the same. Thirty-eight of the control and forty-three of the infants treated with potassium were under 6 months of age. Of the patients receiving potassium therapy, 18 per cent showed either Flexner bacilli or *Proteus morganii* in the stools. The proportion of dysentery cases in the control group cannot be stated, because the stool cultures were not taken in as satisfactory a manner.

The reader is referred to Cases 5 and 6 of the accompanying paper[3] for the details of the course in two extremely sick infants treated with potassium.

Chart 1 shows the number of cases in the control and experimental groups, together with the mortality. In the control series, six cases must be excluded because their deaths were associated with the following conditions in addition to diarrhea: (1) Sepsis due to alpha streptococcus, to *Escherichia coli,* to *Bacillus pyocyaneus,* and to hemolytic *Staphylococcus aureus;* (2) prematurity in two infants weighing less than 1,300 Gm. The corrected mortality of the control series is, therefore, 17 of 53 cases. The records of the 17 fatal cases reveal nothing characteristic. The deaths occurred at varying intervals after therapy was started and the manner of exitus showed no characteristic features.

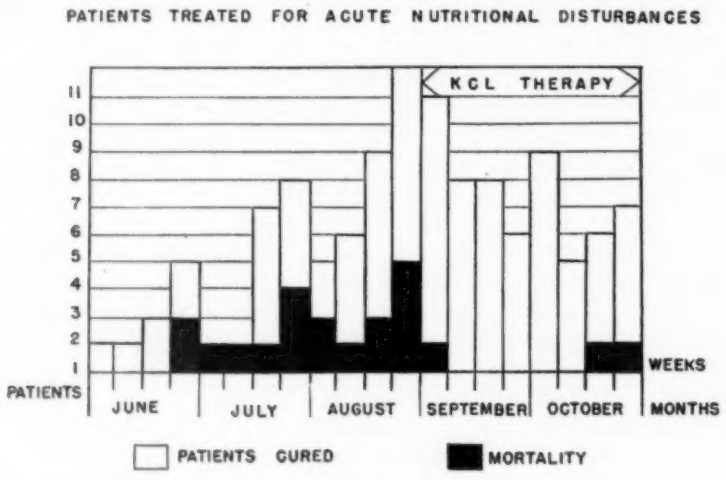

Chart 1.

In the group treated with potassium, one patient died of sepsis due to *B. pyocyaneus* as revealed by a heavy growth in the culture taken from the blood on admission. This organism was grown in practically pure culture from the infant's intestines and at autopsy, ulceration of both the small and large intestine was found. The premature infant listed in Table I weighed 1,300 Gm. and died thirty-six hours after entering the hospital and receiving potassium therapy. Excluding these two cases, the corrected mortality in the cases with potassium therapy was 3 of 50 patients.

The three fatal cases of the potassium series are of interest. The first death occurred in an infant, aged 5 months. The baby showed marked dehy-

TABLE I. MORTALITY IN DIARRHEA

	CONVENTIONAL THERAPY	POTASSIUM THERAPY
Total patients	59	52
Deaths with sepsis	4	1
Deaths with prematurity	2	1
Uncomplicated cases	53	50
Uncomplicated deaths	17	3

dration on admission and died six hours after admission to the hospital. The second death occurred in an infant, aged 25 days. Before admission to the hospital he had had diarrhea for four days. He had been exposed to an epidemic of diarrhea in newborn infants in which four others died. In the hospital, the diarrhea continued for eighteen days. The third death occurred in an infant, aged 3 months, suffering from congenital syphilis as well as diarrhea. The diarrhea had apparently responded satisfactorily to treatment and he received penicillin for the syphilis. The diarrhea had been absent for five days and he was scheduled for discharge the following day. However, he died suddenly and unexpectedly during the night. While he did pass two loose stools during the night, diarrhea was not considered the cause of the death. No autopsy was performed.

Chart 1 shows the mortality per week during the summer. It will be seen that the potassium therapy was instituted during the maximum incidence of diarrhea and at a time when the mortality was high. It is striking to observe that only one of the first forty-two patients treated with potassium died. This favorable record occurred in September, when the mortality from diarrhea is usually high in Baltimore.

COMPLICATIONS OF TREATMENT WITH POTASSIUM CHLORIDE

Potassium Intoxication.—It had been anticipated that potassium intoxication might be encountered. The concentration and total dose of the solution used were calculated to give from 3 to 4 mM of potassium in the maximal amounts recommended for twenty-four hours.[3] If none of this potassium were excreted or transferred in unusual amounts to the intracellular fluids, the rise in concentration of potassium in the serum would be 4 to 5 mM per liter. If the initial serum concentration were 5 mM per liter, the final concentration would be just below that producing heart block. The potassium chloride-sodium chloride-lactate solution has the following concentrations:

K	35 mM per liter
Na	122 mM per liter
Cl	104 mM per liter
Lactate	53 mM per liter

It can be made according to either of the following formulas:

I.		II.	
KCl	2 Gm.	KCl	2 Gm.
Nacl	3 Gm.	NaCl	3 Gm.
Molar sodium lactate	40 c.c.	⅙ molar sodium lactate	250 c.c.
Water	710 c.c.	Water	500 c.c.

The solutions can be autoclaved or the sodium chloride and potassium chloride can be sterilized by dry heat and added to water, together with one 40 c.c. ampule of commercially prepared molar sodium lactate.

Table II shows the concentrations of potassium in the serum of six patients receiving the potassium chloride-sodium chloride-lactate solution. The concentrations were those obtained from serum taken about two hours after finishing the injection of about 80 c.c. per kilogram of body weight over a

period of from four to eight hours. Three values are moderately elevated, but well below the level associated with heart block (10 to 12 mM per liter). In several patients, normal electrocardiograms were obtained during or within two hours following the injection of potassium chloride-sodium chloride-lactate solution.

TABLE II. EFFECT OF SUBCUTANEOUS INJECTION OF 80 C.C. PER KILOGRAM OF BODY WEIGHT OF POTASSIUM CHLORIDE-SODIUM CHLORIDE-LACTATE SOLUTION

CASE	POTASSIUM CONCENTRATION mM per L. of serum
1	3.74
2	4.00
3	6.87
4	3.40
5	6.75
6	6.54

In one patient, potassium intoxication occurred and almost led to death. The infant, aged 12 days, had had diarrhea for two days before admission. During the first three days in the hospital, the potassium chloride-sodium chloride-lactate mixture was administered parenterally. At this time the diarrhea had ceased and the potassium therapy was discontinued. Feedings were given for the next seven days, and the infant's condition seemed to be improving. However, on the eleventh day, the diarrhea recurred. The potassium chloride-sodium chloride-lactate solution was again injected subcutaneously. Within one hour, the infant became cyanotic owing to heart failure. Complete heart block with a rate of about forty per minute was demonstrated by electrocardiogram. At this time the concentration of potassium in the serum was 12.3 mM per liter. Following an intravenous injection of 15 c.c. of 10 per cent solution of calcium gluconate (Smith's) and 150 c.c. of 17 per cent solution of glucose, the cyanosis disappeared, the heart rate increased, and the circulation improved almost immediately. The electrocardiogram was improved one hour later and was normal two hours later. The case will be reported in an accompanying paper.[6] The cause of the rise in serum potassium is not clear in this case. The potassium chloride-sodium chloride-lactate solution was given immediately on recurrence of the diarrhea in this case and later it was apparent from the chart that the baby had been passing very little urine at this time. Furthermore, this baby probably had no deficit of potassium when the second treatment was started, because the initial treatment and the food had replenished the intracellular fluids, and because the relapse had not been of sufficient duration to induce a second deficit of potassium.

It was the developments in this case in particular that led the authors to institute the treatment of paragraph 1 before starting the potassium chloride-sodium chloride-lactate solution. There are other findings which indicate that parenteral potassium should not be started precipitously. In two patients before treatment, the concentration of potassium in the serum was 7 and 9 mM per liter. In connection with several other patients in New Haven moribund from diarrhea, one of the authors (D. C. D.) has observed equally high concentrations of potassium in the serum. As demonstrated in the metabolism

study and actually found by tissue analysis in some of these cases, the intracellular fluids of all these patients were probably low in potassium. The high concentration of potassium in the serum of patients in the advanced stage of dehydration is probably dependent on two factors: (1) The oliguria accompanying dehydration undoubtedly diminishes urinary excretion; (2) when the circulatory failure reaches the degree causing shock, serum concentration of potassium is apt to rise. This observation has been made repeatedly in shock and a recent study shows that this event occurs owing to a loss of potassium from the tissues.[5] Thus it is desirable to replenish intracellular potassium, but one must not accomplish this end under conditions leading to a high concentration of potassium in the serum.

The authors do not believe there is a great deal of danger of potassium intoxication following the injection of potassium chloride-sodium chloride-lactate solution if the following precautions are observed: (1) The dose should seldom be over 80 c.c. per kilogram per day; (2) the rate of injection should not be greater than necessary to give the indicated amount in four hours, and from eight to twelve hours should be employed as a rule; (3) evidence of urine excretion should be obtained before starting the injection of the potassium chloride-sodium chloride-lactate solution; and (4) the solution should not be given until the measures employed in shock have produced some recovery in the circulation and the functioning of the enzyme systems of the cells. Recent studies have emphasized that when the anoxia of shock reaches a certain degree, a number of enzymes in the liver cease to function. When this occurs, potassium may be lost from the liver.[7] Similar events probably take place in other tissues. Hence potassium may not readily be retained in the tissues while the anoxia of poor circulation persists, despite the fact that there is probably a deficit in the intracellular fluids.

Erythema With Desquamation.—Five patients developed striking, generalized erythema on the second or third day of parenteral treatment with potassium chloride-sodium chloride-lactate solution. Three to five days after the erythema, the skin became roughened and desquamated. Otherwise these patients did not appear to differ from the others. No serum potassium concentrations or electrocardiograms were taken on these patients at the time of the erythema. Although the dilatation of the capillaries may have been produced by a rise in the concentration of serum potassium, the exact cause of this phenomenon cannot be stated. In general, the patients receiving potassium show the normal, rosy color of the skin at a time when pallor is the rule when solutions containing no potassium are used. These phenomena need further investigation.

COMMENT

The difference in mortality in the two series is highly significant as measured by the Chi square test. The clinical improvement impressed all observers that the potassium therapy enabled the babies to appear relatively well sooner than when the conventional therapy was used. The duration and intensity of the diarrhea was not apparently altered by the potassium administration.

Since the present study was finished, further trials with potassium chloride-sodium chloride-lactate have been carried out with equally successful results. It is felt that further study will show that parenteral therapy is not necessary after twenty-four hours, if the initial treatment has restored extracellular electrolyte and partially restored intracellular potassium. Recently the potassium chloride-sodium chloride-lactate solution has been given by mouth after the outlined treatment has been carried out for twenty-four hours; the solution is given in a mixture of equal parts of the potassium chloride-sodium chloride-lactate mixture, water, and 5 per cent solution of glucose. About 150 c.c. per kilogram of body weight is offered per day. The oral fluid is divided into suitable amounts to be ingested every three to four hours. This procedure apparently enables the patients to replace any further loss of electrolyte during the period of fasting, while the stools are still watery. One of the authors (D. C. D.) had tried to institute milk feedings fortified with potassium chloride at an earlier stage than is indicated by previous experience with the conventional type of treatment. The results were not such as to suggest that potassium therapy will permit milk feedings to be resumed at an earlier stage of the treatment than has been customary. In general, the potassium therapy does not apparently shorten the period of watery diarrhea, but it does enable the babies to withstand a severe or prolonged attack that would otherwise be fatal. One of the imponderable advantages of the treatment may have been that it has given the authors the courage and confidence in the final outcome which led to a sufficiently long period of fasting.

A dogmatic outline for the treatment of diarrhea is presented elsewhere.[8] It is realized that further work is necessary to show the best way of giving potassium chloride, along with sodium chloride, and sodium lactate (or sodium bicarbonate). There can be no doubt that the treatment of the future will take into account the results presented in this and the previous paper,[3] and that the mortality of infants suffering from the severe dehydration of diarrhea can be reduced to a much lower figure than has been the case in the last twenty years.

SUMMARY

A new plan for the treatment of diarrhea in infants is described. The various procedures which have been employed during the past twenty years are followed except that replenishment of body electrolyte is accomplished by adding potassium chloride to the solutions containing sodium chloride, sodium lactate, and glucose. In all severely ill patients, blood or plasma infusions are also carried out.

The results obtained with the new treatment in the last half of the diarrhea season are compared with the results obtained with the old treatment during the first half of the diarrhea season. The two series of cases were of comparable severity. With the new treatment 3 of 50 patients died; with the conventional treatment 17 of 53 patients died. The decrease in mortality was not accompanied by a shortening of the duration or a decrease in intensity of the diarrhea. Administration of potassium chloride in conjunction with the

other established procedures enables the babies to recover from some attacks of diarrhea that would otherwise be fatal.

Two complications of the new treatment were encountered: (1) Potassium intoxication with complete heart block developed once, but recovery followed treatment. (2) Five patients developed intense erythema followed by desquamation. While this complication did not otherwise alter the course, it is probably a consequence of the new treatment.

The precautions necessary for the prevention of potassium intoxication are briefly discussed.

REFERENCES

1. Powers, G. F.: Am. J. Dis. Child 32: 232, 1926.
2. Hartmann, A. F., Perley, A. M., Basman, J., Nelson, M. V., and Asher, C.: J. PEDIAT. 13: 692, 1938.
3. Darrow, Daniel C.: J. PEDIAT. 28: 515, 1946.
4. Wilhelmi, A. E., Russell, J. A., Engel, M. G., and Long, C. N. H.: Am. J. Physiol. 144: 674, 1945.
5. Fox, C. L., and Keston, A. S.: Surg. Gynec. & Obst. 80: 561, 1945.
6. Govan, Clifton D., Jr., and Weiseth, Warren M.: J. PEDIAT. 28: 550, 1946.
7. Darrow, D. C., and Engel, F. L.: Am. J. Physiol. 145: 32, 1945.
8. Darrow, D. C.: Treatment of Dehydrations Due to Infantile Diarrhea. Interne. To be published.

POTASSIUM INTOXICATION

Report of an Infant Surviving a Serum Potassium Level of 12.27 Millimoles per Liter

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THE recent studies of Darrow[1] and Govan and Darrow[2] have demonstrated the value of potassium in the treatment of dehydration resulting from diarrhea. The therapeutic use of potassium is without danger provided the concentration of this ion in the extracellular fluid is not excessively elevated. Ringer and Murrell,[3] and Howell[4] were first to demonstrate the inhibitory effect of the potassium ion upon the heart. Winkler and associates[5] have studied the electrocardiographic changes which occur in dogs as the concentration of potassium in the serum is gradually raised. Intraventricular block occurred when the concentration was a little more than doubled, and cardiac arrest occurred at levels of 14 to 16 mM per liter.

Smillie,[6] in 1915, described potassium intoxication in patients receiving potassium therapy. He found that amounts of potassium which did not affect the normal individual produced severe effects in a patient with impaired renal function. Following this initial report, numerous cases of potassium poisoning have been described, yet no recovery has been recorded following elevation of the serum potassium to concentrations of more than 12 mM per liter.

REPORT OF A CASE

In September, 1945, a 12 day-old white girl (D. L. J., No. 43515) was admitted to the Harriet Lane Home because she had had watery diarrheal stools for two days prior to admission. The family history was noncontributory to the present illness. The birth was uncomplicated and spontaneous. The infant was exposed, in a nursery, to an epidemic of diarrhea of the newborn. At the age of 10 days the infant began to have greenish liquid stools. The following day the diarrhea became more severe and continued on the twelfth day, when she was brought to the Harriet Lane Home.

Physical Examination.—The physical examination revealed a dehydrated, emaciated but alert infant who was acutely ill. There was loss of skin turgor, depression of the anterior fontanel, and the eyes were sunken. The heart was normal in rate and rhythm, and no adventitial sounds were heard. The abdomen was flat and the liver edge was barely palpable. Neither the spleen nor the kidneys were felt. The genitals appeared normal. Scattered over the arms and legs was a splotchy red papular eruption. On the palms and soles were numerous large bullous impetiginous lesions.

Course.—The infant was isolated and during the first three days of hospitalization was given nothing by mouth. During this period the infant was given, intravenously and subcutaneously, 100 c.c. per kilogram of body weight of a solution having approximately the following composition:

K	35 mM per liter
Na	122 mM per liter
Cl	104 mM per liter
Lactate	53 mM per liter

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In addition, sufficient 5 per cent glucose solution was administered intravenously to bring the fluid intake to 200 c.c. per kilogram of body weight per day. Toward the end of the third hospital day the stools were normal and the general condition had improved. On the fourth hospital day a feeding mixture of equal parts of skimmed milk and lactic acid milk with 5 per cent dextrimaltose added was given. From this day until the ninth hospital day the caloric intake was gradually increased until the baby was receiving 60 calories per kilogram of body weight.

On the tenth hospital day the infant again began to have frequent large watery stools. Between 6 A.M. and 12 noon on the eleventh hospital day the baby had six large liquid stools and began to show evidence of dehydration despite a fluid intake of 175 c.c. of fluid per kilogram of body weight per day. The feeding was discontinued and 200 c.c. of the potassium chloride-sodium chloride-lactate solution were injected subcutaneously, without any preceding administration of salt solution.

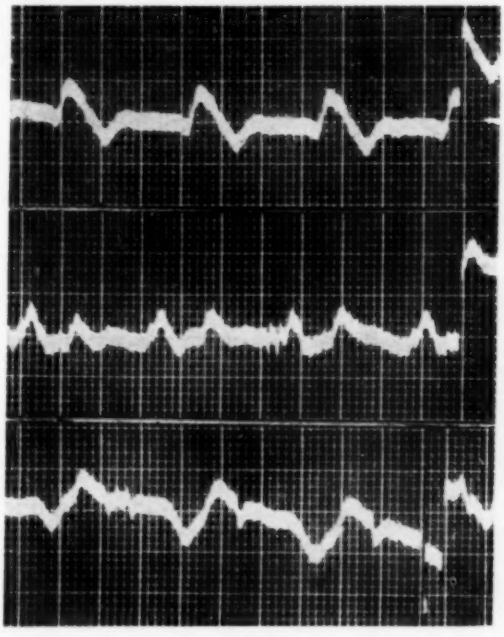

Fig. 1.

One hour later the baby appeared to be in shock. Examination revealed the skin to be a grayish color, she was listless and had a very feeble cry, the extremities were cold, and the heart rate was 80 per minute. An electrocardiogram (Fig. 1) taken at this time revealed evidence of first degree heart block, intraventricular block, pathological T waves in all leads, depression of the S-T segment, absence of the P waves in Lead I, and low voltage. These changes are typical of those described by Winkler, Hoff, and Smith[5] as representing severe potassium intoxication. Blood was drawn at this time for a serum potassium determination. The condition of potassium poisoning was recognized on clinical grounds and the infant was promptly given 15 c.c. of calcium gluconate intravenously and 150 c.c. of hypertonic glucose solution. Within a few minutes she seemed to respond to this therapy. She was then given a transfusion of whole blood. One hour after therapy was started, a second electrocardiogram (Fig. 2) revealed partial recovery. The heart rate at this time had risen from 80 to 110 per minute. There was no evidence of intraventricular block and the T waves in Lead I were normal. Heart block was still evident and the

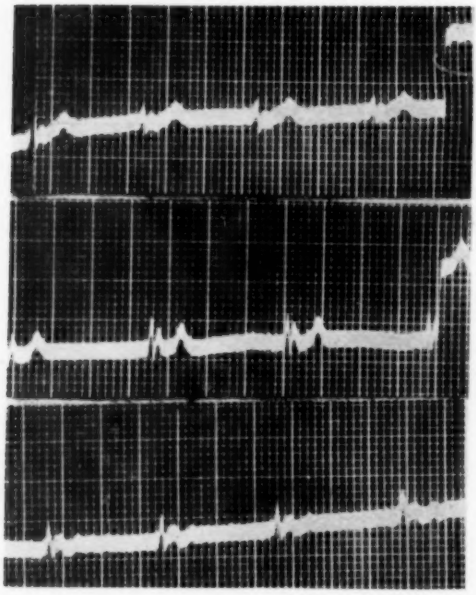

Fig. 2.

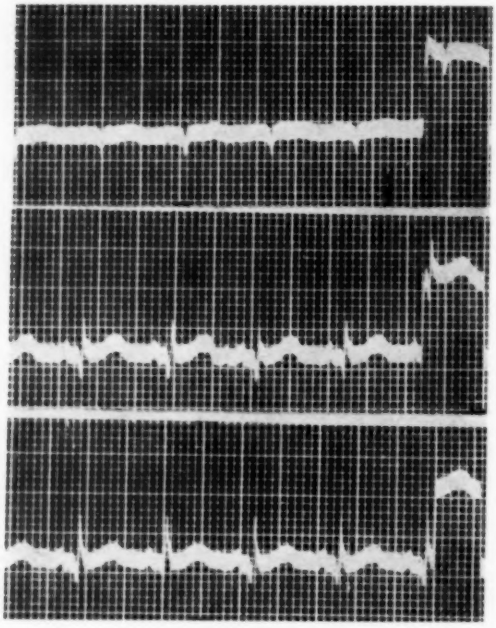

Fig. 3.

P waves were isoelectric in Leads I and II. Two hours after the initial therapy, a third electrocardiogram was taken. This showed complete recovery in Leads II and III. Technical difficulties were responsible for the effect seen in Lead I. The serum potassium level determined on the blood sample taken just prior to treatment proved to be 12.3 mM per liter. The infant continued to improve and was discharged two weeks later in good condition.

DISCUSSION

The potassium intoxication evident in this 3-kilogram infant was manifest one hour after a subcutaneous infusion of 200 c.c. of the potassium chloride-sodium chloride-lactate mixture. The amount of potassium (8 mM) administered, even if it had been absorbed immediately, was enough to raise the extracellular potassium concentration only 5 mM per liter. Yet, at the onset of the intoxication, the serum potassium level was 12.27 mM per liter. The potassium administered to the infant during the first diarrheal episode may have replaced any deficit of cellular potassium and allowed potassium to accumulate in the extracellular fluids. It is, therefore, possible that this infant was given an injection of potassium at a time when the concentration of potassium in the serum was already high. The oliguric state was also a contributing cause. The baby was known not to have voided for five hours before the parenteral potassium was administered.

The first signs of the intoxication were the onset of cyanosis and clinical signs of shock, which resulted from the slowed circulation secondary to the brachycardia and heart block. Improvement in the infant's color and an increase in the heart rate immediately followed the intravenous injections of calcium gluconate and hypertonic glucose solutions. Within one hour the infant was clinically asymptomatic, although minor changes in the electrocardiogram persisted. At the end of two hours the electrocardiogram was normal.

In treating this infant, the calcium ion was supplied to counteract the inhibitory effect of potassium upon the heart.[8] The hypertonic glucose was given not only as a diuretic but also to enhance the deposition of glycogen in the liver. Fenn[9] has demonstrated that when glycogen is deposited in the liver it is accompanied by potassium and water. It was thought that the injection of a hypertonic glucose solution would stimulate glycogen deposition in the liver and thus reduce the concentration of potassium in the extracellular fluids. This case demonstrates that prompt and specific therapy will relieve severe potassium intoxication.

SUMMARY

An infant suffering with potassium intoxication recovered following the intravenous injection of calcium gluconate and hypertonic glucose solutions.

REFERENCES

1. Darrow, Daniel C.: J. Pediat. 28: 515, 1946.
2. Govan, Clifton D., Jr., and Darrow, Daniel C.: J. Pediat. 28: 541, 1946.
3. Ringer, S., and Murrell, W.: J. Physiol. 1: 72, 1878.
4. Howell, W. H.: Am. J. Physiol. 15: 280, 1906.
5. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Am. J. Physiol. 124: 478, 1938.
6. Smillie, W. G.: Arch. Int. Med. 16: 330, 1915.
7. Harrison, H. E., and Darrow, D. C.: J. Biol. Chem. 121: 631, 1937.
8. Ringer, S.: J. Physiol. 4: 29, 1883.
9. Fenn, W. O.: J. Biol. Chem. 128: 297, 1939.

HOT BATHS IN THE TREATMENT OF EARLY INFANTILE PARALYSIS

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IMMERSION in warm water during the early phases of infantile paralysis has been used for some time and has been described by different authors for relief of soreness and muscle tightness,[1-4] but this approach has never been widely applied. Our results obtained so far with this method seem to us to justify the re-emphasis of this simple procedure.

We would like to do this with all the reserve necessarily needed for the recommendation of any treatment approach in infantile paralysis at the present time. The symptoms in this disease vary widely; spontaneous recoveries are frequent. The possible value of any treatment form can be determined only by the comparison of large groups of similar cases treated in different ways and uniformly recorded. We are lacking in sufficient numbers and necessary controls to draw valid conclusions; but we feel that the number of our patients is large enough to derive a clinical impression of the value of the treatment approach we are reporting.

We have treated all patients with infantile paralysis with Kenny packs in the 1941, 1942, and 1943 outbreaks. It was our impression that muscle soreness and stiffness responded more quickly in a large percentage of patients than with previously employed methods. Each year, however, a number of patients were observed in whom pain and stiffness remained in spite of long periods of packing. In November, 1943, we decided to treat several patients, who remained tender and very stiff in spite of prolonged packs, with frequent daily immersions in hot water. We observed a definite spurt in loosening up and decreased pain. Gradually we prescribed this treatment to an ever-increasing number of patients.

After January, 1944, hot baths became the treatment of choice and packs were prescribed only for those patients who for one reason or another could not be put into the pool; for instance, because of the patient having to wear a plaster boot, or because of incontinence. Until Sept. 1, 1945, we have treated 307 patients.

The technique we are using is as follows: Patients are put into water of a temperature of 104° F. The water is shallow so that the patient can lie flat with his head only very slightly raised on a headrest (Fig. 1). Gentle, free motion is not restricted but no exercises of any kind are given.

The lifting is done either on light canvas stretchers or by two to four persons according to the patient's height, leaving the patient's body straight to prevent pull on tender muscles (Fig. 2). Immersions are started as soon as the patient has been admitted—usually from an isolation hospital. For pa-

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tients with marked stiffness and tenderness, we prescribed six immersions a day, lasting fifteen to twenty minutes each. As pain and stiffness subside, the number of immersions is gradually reduced. Bathing caps protect the hair from getting wet and ear plugs are inserted to protect the ears. At the end of each immersion, the patient is thoroughly dried and wrapped in wool blankets. Systemic reactions are carefully watched for during the first two weeks. Rectal temperature readings are taken following each immersion.

Fig. 1.

Fig. 2.

Blond, fair-skinned children may develop temperatures up to 101° F., but these will return to normal in all cases within an average of fifteen minutes. All patients receive from 2 to 8 Gm. of salt tablets daily according to their weight, and their fluid intake is forced.

Other treatment procedures such as re-educational or passive exercises are given during interval periods. If passive stretching is indicated, it is given immediately following the hot bath.

As we have been putting large numbers of patients into pools simultaneously, incontinence of feces or urine precluded this form of treatment for some. If individual baths could have been used, these patients also could have had immersions.

Fig. 3.—Case 1, J. T. Onset Aug. 14, 1943. Date of photograph Feb. 14, 1944.

Several patients developed colds while undergoing this treatment, but in looking over the case incidence and comparing it with the incidence of colds in other years during the same period, we found that the number of colds had not increased. Children with discharging or sensitive ears are protected with particular care from getting water into the auditory canals.

In order to get objective findings and to leave as little room as possible for subjective interpretations on the part of the individual examiner, we have tried to establish a routine of examination for our patients. Flexibility and muscle tightness are recorded in angles of motion and distance in inches. Tenderness and pain are recorded at rest, in response to pressure and to stretching, and graded as 0, ±, 1+, to 4+. Muscles are tested regularly according to the Lovett system.

Fig. 4.—Case 1, J. T. Date of photograph March 31, 1944.

Fig. 5.—Case 1, J. T. Date of photograph June 9, 1944.

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREATMENT	DAYS OF POOL TREATMENT			
					13	34	46	61
Case 1, J. T.	1	155	Head	Could be lifted 2½"	Rigid	Slightly rigid	Free	Free
History no. 3154								
Age: 5 years					140°			
Sex: male			Trunk flexion: knees straight	130°	110°	100°	90°	90°
Date of onset:			Forehead to knees: knees straight	23"	22"	13"	0"	0"
Aug. 14, 1943			Forehead to knees: knees bent	18"	11"	5"	0"	0"
			Shoulders	Pulled up, cupped ++	+	+	0	0
			Back	Held rigid +++	++	++	++	+
			Straight leg raising: right	135°	110°	100°	100°	95°
			left	125°	115°	105°	105°	95°
			Hip flexion: right	90°	70°	50°	Free	Free
			left	90°	70°	50°	Free	Free
			Knee flexion: right	115°	95°	85°	90°	70°
			left	110°	95°	90°	90°	70°
			Ankle dorsiflexion: right	100°	95°	95°	85°	85°
			left	105°	100°	100°	95°	95°
			Pain to stretching	3+	2+	+	0	0
			Pain to pressure	+	+	0	0	0

Comment: Had prolonged intensive packs with only little improvement in stiffness, and continued marked pain; with hot pools he loosened up slowly but consistently (Figs. 3 to 5). (This is one of the original cases responsible for our starting hot pool therapy.)

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREATMENT	DAYS OF POOL TREATMENT		
					17	33	57
Case 2, C. S. History no. 3144 Age: 15 years Sex: female Date of onset: Sept. 9, 1943	4	103	Neck flexion	Free	Free	Free	Free
			Trunk flexion: knees straight	130°	90°	90°	90°
			Forehead to knees: knees straight	25″	15″	9″	3″
			Forehead to knees: knees bent	14″	4″	0″	0″
			Back	Mild curve in lower dorsal and cervical spine	Seemed straight	Straight	Straight
			Upper extremities	Free	Free	Free	Free
			Straight leg raising: right	135°	115°	90°	90°
			left	140°	115°	95°	90°
			Knee flexion: right	30°	Free	Free	Free
			left	30°	Free	Free	Free
			Ankle dorsiflexion: right	85°	Normal	95°	85°
			left	105°	Could not be tested—sprained ankle	105°	105°
			Pain to stretching	0	0	0	0
			Pain to pressure	0	0	0	0

Comment: Had prolonged packs with only slow and partial improvement of tightness; started to loosen up immediately after hot pools were instituted.

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREATMENT	DAYS OF POOL TREATMENT			
					24	47	54	87
Case 3, B. P. History no. 3357 Age: 13½ years Sex: female Date of onset: Aug. 20, 1944	1	50	Neck flexion	Slightly stiff	Free	Free	Free	Free
			Trunk flexion: knees straight	125°	100°	100°	90°	90°
			Trunk flexion: knees bent	100°	90°	90°	80°	80°
			Forehead to knees: knees straight	35″	26″	14″	7½″	6″
			Forehead to knees: knees bent	34″	6″	0″	0″	0″
			Shoulder abduction: right	60°	70°	45°	55°	55°
			left	70°	80°	80°	80°	90°
			Elbow flexion: right	30°	Free	Free	Free	Free
			left	35°	Free	Free	Free	Free
			Hip flexion: right	60°	Free	Free	Free	Free
			left	70°	Free	Free	Free	Free
			Straight leg raising: right	130°	90°	90°	90°	90°
			left	125°	100°	90°	90°	90°
			Knee flexion: right	Free	Free	Free	Free	Free
			left	Free	Free	Free	Free	Free
			Ankle dorsiflexion: right	90°	80°	80°	80°	80°
			left	90°	80°	80°	80°	80°
			Pain to stretching	4+	2+	0	0	0
			Pain to pressure	2+	0	0	0	0

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREATMENT	DAYS OF POOL TREATMENT			
					12	36	50	69
Case 4, A. G. History no. 3288 Age: 8 years Sex: male Date of onset: July 28, 1944	1	34	Trunk flexion: knees straight	165°	140°	120°	110°	90°
			Trunk flexion: knees bent	95°	90°	90°	90°	90°
			Forehead to knees: knees straight	30″	21″	19½″	12″	5″
			Forehead to knees: knees bent	19″	10″	6½″	0″	0″
			Shoulders	Right elevated	Right elevated	Right elevated	Right elevated	Slight elevation persisted
			Back	Rt. up. dorsal curve	Rt. up. dorsal curve	Rt. up. dorsal curve	Rt. up. dorsal curve	Slight curve persisted
			Hip flexion: right	60°	50°	30°	Free	Free
			left	70°	60°	40°	Free	Free
			Straight leg raising: right	150°	150°	130°	125°	90°
			left	145°	140°	120°	120°	90°
			Ankle dorsiflexion: right	90°	Free	Free	Free	Free
			left	95°	95°	105°	Plaster	90°
			Pain to stretching	3+	2+	0	0	0
			Pain to pressure	3+	2+	0	0	0

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREATMENT	DAYS OF POOL TREATMENT				
					9	25	45	56	108
Case 5, P. S. History no. 3327 Age: 9 years Sex: female Date of onset: Aug. 26, 1944	1	17	Trunk flexion: knees straight	165°	160°	130°	100°	100°	90°
			Trunk flexion: knees bent	130°	100°	90°	85°	85°	85°
			Forehead to knees: knees straight	35″	33″	27″	21″	10″	0″
			Forehead to knees: knees bent	36″	29″	13″	4″	0″	0″
			Hip flexion: right	100°	90°	70°	40°	20°	Free
			left	95°	90°	60°	30°	Free	Free
			Straight leg raising: right	160°	155°	140°	120°	105°	90°
			left	165°	160°	145°	115°	90°	90°
			Knee flexion: right	85°	30°	Free	Free	Free	Free
			left	85°	35°	Free	Free	Free	Free
			Ankle dorsiflexion: right	120°	110°	110°	110°	105°	95°
			left	120°	110°	105°	95°	95°	95°
			Pain to stretching	4+	3+	1+	0	0	0
			Pain to pressure	4+	2+	0	0	0	0
			Was extremely tender; pain and stiffness subsided gradually						

	PACKS STARTED DAYS AFTER ONSET	NUMBER OF DAYS CONTINUED	FLEXIBILITY	FLEXIBILITY BEFORE STARTING POOL TREATMENT	DAYS OF POOL TREATMENT			
					8	14	28	56
Case 6, B. A. History no. 3338 Age: 8½ years Sex: female Date of onset: Aug. 17, 1944	1	30	Neck flexion	Slightly stiff	Free	Free	Free	Free
			Trunk flexion: knees straight	160°	130°	115°	105°	90°
			Trunk flexion: knees bent	95°	90°	90°	85°	85°
			Forehead to knees: knees straight	32″	25″	19″	12″	0″
			Forehead to knees: knees bent	20½″	11″	0″	0″	0″
			Hip flexion: right	Free	Free	Free	Free	Free
			left	90°	40°	Free	Free	Free
			Straight leg raising: right	160°	140°	120°	100°	90°
			left	170°	135°	115°	100°	90°
			Knee flexion: right	Free	Free	Free	Free	Free
			left	30°	Free	Free	Free	Free
			Ankle dorsiflexion: right	100°	95°	90°	90°	90°
			left	105°	100°	100°	100°	100°
			Pain to stretching	4+	2+	±	0	0
			Pain to pressure	4+	2+	±	0	0

Until Sept. 1, 1945, we have treated 35 patients with onset in 1943, 242 with onset in 1944, and 30 with onset in 1945.

All patients of the 1943 outbreak had prolonged periods of packs before they were put into hot water. This group is valuable because it allows us to compare the responses of the patient to packs and to baths. It was our impression, as stated before, that the immersions in hot water speeded up the process of relaxation and elimination of pain from stretching. The case reports illustrate this point.

COMMENT

In spite of having used the technique described for nearly two years, we are making this report only hesitantly and in the form of a preliminary one. We feel, however, that by now we have gained enough information to warrant this communication—especially in order that new victims of infantile paralysis might benefit by our experience.

If one considers, from a purely practical point of view, the relative ease with which baths or hot packs can be given, one will find that the application of hot baths is simpler, especially in patients' private homes or in institutions not especially equipped for the treatment of infantile paralysis. In order to give effective hot packs, four prerequisites are essential which, in our experience, are not often found simultaneously. These are:

1. Ability to determine exact location of so-called spasm
2. Good heating equipment for packs at bedside of patient
3. Correct technique in applying these packs
4. Two workers

Hot baths, on the other hand, will cover any area of muscle tightness regardless of exact location. The equipment consists of a bathtub of sufficient length so that the patient can lie in an extended position. It requires from two to four people to lift the patient in and out of the bath; therefore, the treatment can be given wherever there is a sufficiently long tub and enough help to lift the patient in and out.

In comparing our treatment results, it is our impression that hot baths relieve muscle soreness and tightness faster and more effectively than Kenny packs. Subjectively, the patients prefer the pool treatment, and nearly all of those who had both, and who were old enough to express an opinion, felt that their pain was relieved more rapidly by the baths.

We have adhered so far to one standard technique in order to get an impression with a sufficient number of patients. It is possible that the temperature of 104° is not the optimum one. We will have to try higher and lower temperatures. In view of the fact that mild fever therapy has been reported to be beneficial in relieving soreness and tightness,[5] it may be that the element of raising the patient's temperature may be an important one. On the other hand, beneficial results have been reported using body temperature only.[4] Whether the effect of mineral water is of importance will also have to be evaluated.

We have limited ourselves entirely to the discussion of the uses of hot baths in the treatment of muscle tightness and muscle soreness and have left entirely aside the use of pools in the treatment of the paralysis for ambulation and in re-education of coordinated function, as this is outside the scope of this report.

REFERENCES

1. Lovett, R. W.: J. A. M. A. **78**: 1607, 1922.
2. Legg, A. T.: J. A. M. A. **107**: 633, 1936.
3. Ober, F. R.: J. A. M. A. **110**: 45, 1938.
4. Hipps, H. E., and Crook, B. L.: Arch. Phys. Therapy **25**: 403, 1944.
5. Stone, S.: Arch. Phys. Therapy. **24**: 350, 1943.

THE USE OF NORMAL SERUM GAMMA GLOBULIN ANTIBODIES (HUMAN) CONCENTRATED (IMMUNE SERUM GLOBULIN) IN THE PREVENTION AND ATTENUATION OF MEASLES

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MEASLES in young infants and in debilitated children is often a very serious disease. Therefore, the procurement of either an active or passive prophylactic agent that is easily available, nontoxic on administration, and of uniformly high potency, is urgently needed. The agents heretofore used in passive prophylaxis: convalescent serum, pooled adult serum, normal adult blood, and placental immune globulin, are all deficient in one or more of these categories. Recently Cohn, Oncley, Strong, Hughes, and Armstrong[1] have, in their work on human plasma fractionation, developed a gamma globulin fraction that has been shown by Enders[2] to contain many of the humoral antibodies, and by Stokes, Maris, and Gellis;[3] Ordman, Jennings, and Janeway;[4] Greenberg, Frant, and Rutstein;[5] and Janeway[6, 7] to be highly effective in protecting susceptible children against measles when it is injected shortly after the child is exposed.

Our purpose in this paper is to detail our experiences with the use of this material, normal serum gamma globulin antibodies (human) concentrated (immune serum globulin), in the prevention and attenuation of measles during the past two years. The material used will hereafter be referred to as "gamma globulin."

MATERIAL

Between April 29, 1943, and Aug. 1, 1944, we have administered gamma globulin by intramuscular injection to 267 susceptible children within eight days after exposure to measles for the purpose of preventing or attenuating the disease. Of this group, 113 children were on the pediatric or orthopedic wards of the Gallinger Municipal Hospital, 37 were exposed in nursery schools, and 117 were intimately exposed at home to a sibling with measles.*

RESULTS

1. *Hospital Exposures.*—Measles was very prevalent in Washington in the spring of the years 1943 and 1944, and on fifteen occasions appeared on the pediatric or orthopedic wards of the Gallinger Municipal Hospital. All patients in the same or closely adjacent rooms were considered contacts with measles patients, and all patients treated or visited by one staff member with very early measles were considered contacts, provided the medical history showed that the

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The gamma globulin used in these studies was developed from blood collected by the American Red Cross and produced under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Harvard University. Use of this material was authorized by the Naval Medical School, Bethesda, Md.

*A few of the children exposed at home and at school were treated by us or by the members of the pediatric staff at Gallinger Municipal Hospital. The remainder were the private patients of Drs. William S. Anderson, William F. Burdick, Sander E. Lachman, Joseph S. Wall, John A. Washington, and Dorothy V. Whipple of Washington, D. C., and of Dr. Robert C. Hood of Arlington, Va.

TABLE I. THE RESULTS OF A UNIFORM DOSE OF 2.0 C.C. OF GAMMA GLOBULIN IN PREVENTING MEASLES IN 113 CHILDREN EXPOSED ON THE HOSPITAL WARD

GROUP NO.	DAY AFTER EXPOSURE	NO. PATIENTS TREATED	PATIENTS FOLLOWED 21 DAYS OR MORE					PATIENTS FOLLOWED 10-21 DAYS IN HOSPITAL NO MEASLES	TOTAL NUMBER FOLLOWED			TOTAL NOT FOLLOWED
			TOTAL	IN HOSPITAL		IN CLINIC						
				NO MEASLES	MEASLES	NO MEASLES	MEASLES		NO MEASLES	MEASLES	TOTAL	
1	5	17	14	7	0	6	1*	1	14	1*	15	2
2	3	10	4	4	0	0	0	0	4	0	4	6
3	4	10	5	3	1*	1	0	2	6	1*	7	3
4	4	13	5	4	0	0	1*	2	6	1*	7	6
5	6	10	9	8	0	1	0	1	10	0	10	0
6	2	18	12	4	1†	7	0	2	13	1†	14	4
7	6	4	4	1	0	3	0	0	4	0	4	0
8	4	3	1	1	0	0	0	1	2	0	2	1
9	2	4	1	1	0	0	0	2	3	0	3	1
10	2	5	1	0	1‡	0	0	3	3	1‡	4	1
11	3	5	3	3	0	0	0	0	3	0	3	2
12	5	4	4	4	0	0	0	0	4	0	4	0
13	8	1	1	1	0	0	0	0	1	0	1	0
14	4	4	4	4	0	0	0	0	4	0	4	0
15	6	5	5	3	2*	0	0	0	3	2*	5	0
Total	2–8	113	73	48	5	18	2	14	80	7	87	26

*Modified measles.
†Patient developed measles four days after injection, six days after known exposure.
‡Patient developed measles three days after injection, five days after known exposure.

contact patient had not previously had measles. These patients ranged in age from 5 months to 10 years. Since we were desirous of protecting the wards as completely as possible against further measles, all susceptible contacts were given 2.0 c.c. of gamma globulin. The results are shown in Table I. There were fifty-three children who were observed on the wards for twenty-one days or longer. Of these, two developed measles within four days after receiving the gamma globulin, or six and five days, respectively, after the known exposure. Their measles was of average severity and they must be presumed to have had previous exposure and to have been treated more than eight days after exposure. Three other patients developed measles which was very mild and which apparently was attenuated by the globulin. There were twenty patients who were discharged before the lapse of twenty-one days but who were followed adequately in the outpatient clinic. Two developed mild, apparently modified measles, and eighteen did not. In addition, there were fourteen patients who were in the hospital for periods between ten and twenty days after exposure without developing measles. Our clinic follow-up was not complete, and we are uncertain whether they did or did not develop measles at home. However, they did not succumb while in the hospital and the other hospital patients were spared reexposure. There were twenty-six patients who were discharged within ten days after exposure who were not followed in the outpatient clinic. Thus there were seventy-one patients who were given gamma globulin within eight days after exposure who were observed for twenty-one days or longer with only five cases of measles. Two of the patients who developed measles received globulin on the sixth day after exposure. In all the children the measles was attenuated.

2. *School Exposures.*—These patients are in three groups: In one nursery school there were ten children who were exposed to a patient in the early

catarrhal stage of measles. The exposed children were between 3 and 6 years of age. Five days after exposure each child received 1.0 c.c. of gamma globulin. None developed measles. However, one of these children was exposed at home to a sibling who became ill with measles five days after the school children had received globulin. This child developed a mild measles thirteen days after the second exposure and twenty-seven days after the first exposure. The school was re-exposed by this child. Three day later eleven children received 1.0 c.c. each of gamma globulin. There was no more measles in the school.

In the second group there were ten children between 3 and 5 years of age who played all day with a child with measles. Two days later eight children received 2.0 c.c. each and two children received 1.0 c.c. each of gamma globulin. None of the children developed measles. However, two of the children, aged 3 and 5, again were exposed to a sibling at home ten days after receiving gamma globulin. Both children developed a very mild measles twenty-five days after the first exposure and thirteen days after the home exposure. There were eight children who were re-exposed daily during the pre-eruptive stage of the illness of these boys, twenty-four to twenty-six days after they had received gamma globulin. None of the eight developed measles.

Finally there was a miscellaneous group of six children from 3 to 8 years of age who received 0.5 to 1.0 c.c. of gamma globulin four to eight days after school exposure. Two children, aged 4 and 3 years, who received 1.0 c.c. of gamma globulin each four and eight days after exposure, developed mild measles. Six children did not develop measles.

3. *Home Exposures.*—The experience with these patients is shown in Table II. The children varied in age from 4 months to 16 years. However, there were only six patients 8 years of age or over, only two were 12 years or over, and only one was under 5 months. All injections were given within eight days after exposure. Most of the patients received a dose of 0.5 to 1.0 c.c. that was, in most instances, calculated to modify rather than to prevent the disease. However, of eighty-three patients in this group, forty-eight (57.8 per cent) were completely protected and only four developed average measles. The high incidence of mild measles in the patients receiving between 1.0 and 2.0 c.c. of gamma globulin is undoubtedly accounted for by chance in a small group. Among twenty-three patients who received 2.0 c.c. or more, approximately 87 per cent were protected completely.

TABLE II. RELATION OF THE DOSE OF GAMMA GLOBULIN TO THE DEGREE OF PROTECTION IN 117 CHILDREN TREATED ON OR BEFORE THE EIGHTH DAY AFTER INTIMATE EXPOSURE TO MEASLES AT HOME

DOSE (C.C.)	AGE RANGE	TOTAL PATIENTS TREATED	NO MEASLES	MILD MEASLES	AVERAGE OR SEVERE MEASLES	COMPLICATIONS OF MEASLES
0.5 – 1.0	1/12–11 yr.	83	48	31	4	1 Otitis media
1.25– 1.5	9/12–10 yr.	11	4	7	0	0
2.0 – 3.0	5/12–16 yr.	23	20	2	1	0
Total	1/12–16 yr.	117	72	40	5	1 Otitis media

Re-Exposures.—There have been eight children in this group of 267 who have had intimate home exposure to siblings who developed measles from six to ten days after these eight patients were given gamma globulin. Five were protected from re-exposure, and three developed mild measles. They were as follows: Four children had received 2.0 c.c. of globulin; three were still protected and one developed mild measles from the second exposure. One child, aged 2, had been given 1.75 c.c. of gamma globulin. She was protected from both exposures. Two children had received 1.0 c.c. of gamma globulin. Both developed mild measles from the second exposure, and one child, aged 4, had been given only 0.5 c.c. of gamma globulin but was protected from the original exposure and from exposure to his mother who developed measles approximately one week after he had been immunized. And finally there were eight nursery school children, seven of whom had received 2.0 c.c. and one who had received 1.0 c.c. of gamma globulin, who were re-exposed twenty-four to twenty-six days later. None of them developed measles.

REACTIONS AND COMPLICATIONS

Reactions to the injections of concentrated gamma globulin were most noticeable by their absence. Only one child complained of slight local soreness for a short while, and in another 4-year-old child there was an unexplained subnormal temperature for two weeks. Nor were there any serious complications in the measles that followed the administration of gamma globulin. There were fifty-seven children who developed measles after being treated. In only one was there any complication, an otitis media in a 4-year-old boy who was given 1.0 c.c. of gamma globulin five days after exposure.

COMMENT

The group of patients who have been presented in this paper is too small for definite conclusions. However, certain trends are fairly evident. Gamma globulin, when administered intramuscularly, within seven or eight days after exposure to measles, is a potent prophylactic agent against this disease. While the uniform potency of different lots of the product has not been demonstrated, there is little likelihood of great variation as long as large pools of plasma are used in its manufacture. Nevertheless, exact calculation of the dosage to be employed for attenuation of or complete protection against measles will be very difficult. The age and size of the patient, the intimacy and duration of exposure before treatment, and the susceptibility of the individual patient are all variable factors that cannot be evaluated completely. Stokes, Maris, and Gellis[3] recommend 0.02 c.c. per pound of body weigh for attenuation and 0.08 c.c. per pound for protection. For children of five years and under the dosages are: 0.25 to 0.5 c.c. for attenuation and 2.0 to 2.5 c.c. for protection, and for children from 6 to 12 years 1.0 to 1.5 c.c. for attenuation and 4.0 to 5.0 c.c. for protection. We have shown that for the type of exposure found in nursery schools and kindergartens, 1.0 to 2.0 c.c. of gamma globulin is adequate for complete protection, and that in hospitals a uniform dose of 2.0 c.c. for children 10 years of age or less gives almost complete protection. With children exposed at home the results have

been more variable. There have been a few cases of severe measles, presumably in extremely susceptible individuals, even with large doses of globulin, and attenuation of measles has been somewhat uncertain.

Our results have shown a definite difference from those heretofore reported in this respect. When small doses were used by us, complete protection occurred in 58 per cent of the patients. This is extremely unusual; and cannot easily be accounted for. A considerable number of the children, injected and protected with 1.0 c.c. or less of gamma globulin, were treated by a single observer. It is possible that he failed to record some cases of very mild measles. However, since he used a lot of material not tested elsewhere or by other observers in our group in treating three-fourths of his patients, it is equally possible that he was using material of very high potency. Further observations are needed to evaluate this discrepancy.

SUMMARY

Gamma globulin was given to 267 exposed susceptible children in an effort to attenuate or prevent measles. Final results have been obtained for 241 children. Of these, fifty developed mild or attenuated measles and seven developed average measles. Among sixteen children who were re-exposed six to twenty-eight days after injection, the original treatment gave full protection to thirteen while three developed very mild measles. Only one child developed a complication (acute otitis media). There were no significant reactions to the injections of gamma globulin.

CONCLUSION

Normal serum gamma globulin antibodies (human) concentrated (immune serum globulin) is an effective, apparently nontoxic prophylactic agent for use in preventing or modifying measles.

REFERENCES

1. Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr.: J. Clin. Investigation 23: 417, 1944.
2. Enders, J. F.: J. Clin. Investigation 23: 510, 1944.
3. Stokes, J., Jr., Maris, E. P., and Gellis, S. S.: J. Clin. Investigation 23: 531, 1944.
4. Ordman, C. W., Jennings, C. G., Jr., and Janeway, C. A.: J. Clin. Investigation 23: 541, 1944.
5. Greenberg, M., Frant, S., and Rutstein, D. D.: J.A.M.A. 126: 944, 1944.
6. Janeway, Charles A.: J.A.M.A. 126: 674, 1944.
7. Janeway, Charles A.: Bull. New York Acad. Med. 21: 202, 1945.

THE USE OF NORMAL SERUM GAMMA GLOBULIN ANTIBODIES (HUMAN) CONCENTRATED (IMMUNE SERUM GLOBULIN) IN THE TREATMENT OF PREMATURE INFANTS

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THE prevention of infection constitutes one of the most serious problems associated with the care of prematurely born infants. These infants have few if any humoral antibodies except the small amounts that normally pass the placenta. Consequently, if human antibodies could be made available in concentrated form, they might provide a valuable adjunct to the treatment of such infants. Cohn, Oncley, Strong, Hughes, and Armstrong,[1] in the course of their work on human plasma fractionation, have developed a gamma globulin fraction that was found by Enders[2] to contain a large number of humoral antibodies and was found by a number of other investigators[3-7] to be highly potent agent in the prophylaxis of measles. The question of the possible value of this gamma globulin fraction as a general prophylactic against infection in a nursery for premature infants immediately arose. In an attempt to shed light upon this possibility, we gave gamma globulin to alternate infants who were admitted to the nursery for premature infants in the Gallinger Municipal Hospital from Jan. 1 to Dec. 31, 1944.

The purpose of the present paper is to present a summary of our findings in this study.

PROCEDURE

The material used as a possible prophylactic agent was normal serum gamma globulin antibodies (human) concentrated (immune serum globulin), hereafter called "gamma globulin." The patients treated were prematurely born infants who were admitted to the nursery for premature infants in the obstetric division of the Gallinger Municipal Hospital. In order to obtain a group of viable patients for study, the infants were admitted to the series when they were 24 hours old, thus eliminating infants who were dead or moribund at the end of the first day. Furthermore, all infants who were found on admission, or at any subsequent date, to be suffering from a congenital defect or disease incompatible with normal physical development were excluded from the series, as were a small number of infants whose names were inadvertently omitted from the list. All other infants were included in the study. Alternate infants were given 2.5 c.c. of gamma globulin by intramuscular injections on the second, eighth and

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The gamma globulin used in these studies was developed from blood collected by the American Red Cross and produced under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Harvard University. Use of this material was authorized by the Naval Medical School, Bethesda, Md.

Lieutenants McMain and Antell made their contribution to this paper before entering the Army of the United States.

fifteenth days of life, and every two weeks thereafter until the infant reached a weight of 5 pounds and 8 ounces. This dose, at each injection, corresponded to the gamma globulin from 62.5 c.c. of normal pooled human plasma. The remaining infants received no globulin. The normal diet and the nursing care of the two groups of infants were the same, as was the treatment of sick infants after an illness became manifest.

It must be noted that this study was carried on at a time when, due to wartime shortages, the nursing staff in the nursery was greatly depleted. In consequence, the nursing technique was grossly inadequate, infection was frequent, and the over-all mortality was high.

RESULTS

There were 117 infants who received injections of gamma globulin and 113 who served as controls. The distribution of the two groups of infants according to birth weight, and the gross mortality encountered in each group and in each weight division are shown in Table I. The groups were highly comparable in weight distribution. There was no significant difference in mortality in the two groups, nor any sustained difference in weight in the two groups.

TABLE I. COMPARISON OF BIRTH WEIGHT AND MORTALITY IN PREMATURELY BORN INFANTS WHO DID AND WHO DID NOT RECEIVE INJECTIONS OF GAMMA GLOBULIN

BIRTH WEIGHT*	TOTAL		INFANTS RECEIVED GAMMA GLOBULIN		INFANTS RECEIVED NO GAMMA GLOBULIN	
	NO. OF INFANTS	INFANTS DIED	TOTAL INFANTS	INFANTS DIED	TOTAL INFANTS	INFANTS DIED
2.0 to 2.15¾	9	8	5	4	4	4
3.0 to 3.7¾	17	11	7	5	10	6
3.8 to 3.15¾	25	13	13	8	12	5
4.0 to 4.7¾	34	7	18	3	16	4
4.8 to 4.15¾	56	10	26	7	30	3
5.0 to 5.7¾	89	6	48	2	41	4
Total	230	55	117	29	113	26

*Weight expressed in pounds and ounces.

The morbidity rates for the infants who survived and were discharged from the hospital in good condition are shown in Table II. Since the number of patients is small, all types of illness are grouped together. The high incidence

TABLE II. COMPARISON OF BIRTH WEIGHT AND MORBIDITY IN PREMATURELY BORN INFANTS WHO LIVED, WHO DID AND WHO DID NOT RECEIVE INJECTIONS OF GAMMA GLOBULIN

BIRTH WEIGHT*	TOTAL INFANTS		INFANTS RECEIVED GAMMA GLOBULIN		INFANTS RECEIVED NO GAMMA GLOBULIN	
	NO. OF INFANTS	INFANTS ILL	NO. OF INFANTS	INFANTS ILL	NO. OF INFANTS	INFANTS ILL
2.0 to 2.15¾	1	1	1	1	0	0
3.0 to 3.7¾	6	6	2	2	4	4
3.8 to 3.15¾	12	11	5	4	7	7
4.0 to 4.7¾	27	21	15	11	12	10
4.8 to 4.15¾	46	38	19	16	27	22
5.0 to 5.7¾	83	65	46	36	37	29
Total	175	142	88	70	87	72

*Weight expressed in pounds and ounces.

of illness is accounted for in large measure by the grossly inadequate nursery personnel, and in part by the fact that any deviation from the normal, particularly with regard to gastrointestinal symptoms, respiratory tract symptoms, or general loss of vigor, was considered an evidence of illness. When judged by these standards, there was no appreciable difference in morbidity between infants who were given injections of gamma globulin and those who did not receive the preparation.

The gain in weight was studied as another possible criterion for the value of gamma globulin in the care of premature infants, with the average time to regain the birth weight and the average time to succeed to the normal discharge weight of 5½ pounds being the most objective figures available. The details of this comparison between the two groups of infants under study are shown in Table III. The average time required to reach each goal was slightly less in infants who were treated with gamma globulin, but the differences are so slight that they cannot be regarded as significant.

TABLE III. COMPARISON OF BIRTH WEIGHT, TIME TO REGAIN BIRTH WEIGHT, AND TIME TO GAIN DISCHARGE WEIGHT* IN PREMATURELY BORN INFANTS WHO SURVIVED, WHO DID AND WHO DID NOT RECEIVE INJECTIONS OF GAMMA GLOBULIN

BIRTH WEIGHT†	INFANTS RECEIVED GAMMA GLOBULIN			INFANTS RECEIVED NO GAMMA GLOBULIN		
	NO.	AVG. DAYS TO REGAIN B.W.	AVG. DAYS TO GAIN DISCH. WT.	NO.	AVG. DAYS TO REGAIN B.W.	AVG. DAYS TO GAIN DISCH. WT.
2.0 to 2.15¾	1	43	82	0	–	–
3.0 to 3.7¾	2	34	99	4	40	99
3.8 to 3.15¾	5	32	75	7	27	74
4.0 to 4.7¾	15	26	52	12	29	60
4.8 to 4.15¾	19	25	45	27	26	44
5.0 to 5.7¾	46	25	31	37	29	36
Total	88	26.1	42.1	87	28.4	49.5

*Discharge weight 5 pounds, 8 ounces.
†Weight expressed in pounds and ounces.

SUMMARY AND CONCLUSIONS

Gamma globulin, in doses of 2.5 c.c. (equivalent to the gamma globulin from 62.5 c.c. of normal pooled human plasma) given on the second, eighth, and fifteenth days of life and thereafter every two weeks until a discharge weight of 5 pounds, 8 ounces was reached, was given to 117 prematurely born infants; 113 infants of similar birth weight who received no gamma globulin were studied as control patients. There was no difference in the gross mortality and morbidity rates of the two groups of infants. Likewise, there was no significant difference in the time required for the two groups of infants to regain the birth weight or to attain a discharge weight of 5 pounds and 8 ounces.

REFERENCES

1. Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr.: J. Clin. Investigation 23: 417, 1944.
2. Enders, J. F.: J. Clin. Investigation 23: 510, 1944.
3. Stokes, J., Jr., Maris, E. P., and Gellis, S. S.: J. Clin. Investigation 23: 531, 1944.
4. Ordman, C. W., Jennings, C. G., Jr., and Janeway, C. A.: J. Clin. Investigation 23: 541, 1944.
5. Greenberg, M., Frant, S., and Rutstein, D. D.: J.A.M.A. 126: 944, 1944.
6. Janeway, C. A.: J.A.M.A. 126: 674, 1944.
7. Janeway, C. A.: Bull. New York Acad. Med. 21: 202, 1945.

HEMOLYSIS FROM IRREGULAR ISOAGGLUTININS (COLD AGGLUTININS) FOLLOWING TREATMENT FOR ERYTHROBLASTOSIS FETALIS

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REPORTS of erythroblastosis fetalis, or hemolytic disease of the newborn, have become of such frequency in the recent medical literature that only those which show deviation from the usual course of the disease are worthy of attention. Our reason for this report of an infant suffering from this condition, is that recovery was complicated by the occurrence of cold agglutinins in its blood, that necessitated twenty-two transfusions over a period of three weeks, before recovery was complete.

CASE HISTORY

A female infant, weighing 6 pounds, 11 ounces, was born in the Presbyterian Hospital of a para i mother, following an eight-hour normal labor. The older sister had no abnormal conditions existing at birth or after, and was now 5½ years of age and well. The infant was pale and listless at birth, with a spleen enlarged about one fingerbreadth below the costal margin. Blood examination showed the hemoglobin to be 60 per cent, 3,500,000 red cells, and 24,800 white cells. There were 22 per cent nucleated red cells, both normoblasts and erythroblasts, and 10 per cent myelocytes among the white cells. The infant's blood was Group A, subgroup A_1, Rh positive; the father's blood was Group A_1, Rh positive, and the mother's blood was Group A_1B, Rh negative. The diagnosis of erythroblastosis fetalis was made. We were unable to demonstrate anti-Rh agglutinins in the mother's blood until two weeks after delivery. They were still demonstrable after a year.

Treatment by transfusions was begun within three hours after birth with the results shown in Charts I to III (c.a. standing for cold agglutinins). During the first fifteen days of life, sixteen transfusions were given from the blood of five donors. Four of these donors* were A_1, Rh positive, and one donor was A_1, Rh negative. None of these donors' blood agglutinated the blood of the infant or was agglutinated after incubation at 37° C. for one hour, which we have always assumed to be sufficient in these instances. While the infant's blood was very slightly improved, and the nucleated red cell count fell to 7 per cent, it was impossible to raise it to a satisfactory level. From the increasing icterus, urobilin, and blood cells in the urine, it was obvious that an intense hemolysis was taking place. The icterus index rose to 470 by the ninth day of life, and remained at that level until the sixteenth day of life. During this period the infant took feedings of pooled breast milk well and, except for the intense jaundice, was in fairly good condition.

It was then found that the infant's blood contained irregular isoagglutinins for each of these five donors, that clumped these donors' cells at 0° C., but did not clump the same cells at 20 or 30° C. Two A_1, Rh positive donors were obtained whose blood was not agglutinated by the infant's blood at 0° C. in vitro, and transfusions were given from this blood on the sixteenth day of life. Improvement was immediate. The blood rose to normal levels, the jaundice disappeared within twelve days, and the urobilin and blood cells disappeared from the urine. The nucleated red cells disappeared from the peripheral circulation and reticulocytes began to appear. After receiving twenty-two transfusions, or a total of 2,300 c.c. of blood, the infant was discharged on the thirty-third day of life. The chart shows the condition of the blood through the fifty-eighth day of life. The child is now 3½ years of age and in good health.

*Our laboratory's results of the blood types, Rh factors, and agglutinins were checked by Israel Davidsohn, M.D., of Mount Sinai Hospital, Chicago, whom we wish to thank.

DAY OF LIFE	1	2	3	4	5	6	7	8	9
TRANSFUSIONS CC	50	30	50	50	50	75	50	125	75
DONOR	1Rh+ca	1	1	1	1	2Rh+ca	2	3Rh+ca	3
ICTERUS INDEX			35	125	461	460	465		470
HEMO GLOBIN %	80								
	70								
	60								
	50								
RED CELLS MILLIONS	45								
	35								
	25								
	15								
ERYTHRO BLASTS %	30								
	20								
	15								
	5								
WHITE CELLS THOUSANDS	25								
	20								
	15								
	10								
POLY'S	46	63				60			64
LYMPH	16	21				34			30
MONO	16	2				3			2

Chart I.

DAY OF LIFE	10	11	12	13	14	15	16	17	18
TRANSFUSIONS CC	75	45	80	20	65	60	70	70	75
DONOR	4Rh-ca	4	4	4	5Rh+ca	5	6Rh+	6	6
ICTERUS INDEX		470				468		160	77
HEMO GLOBIN %	70								
	60								
	50								
	40								
RED CELLS MILLIONS	45								
	35								
	25								
	15								
ERYTHRO BLASTS %	15								
	10								
	5								
	1								
WHITE CELLS THOUSANDS	25								
	20								
	15								
	10								
POLY'S	64	53			54	48	55	15	
LYMPH	30	42			39	46	39	78	
MONO	2	3			5	4	1	4	

Chart II.

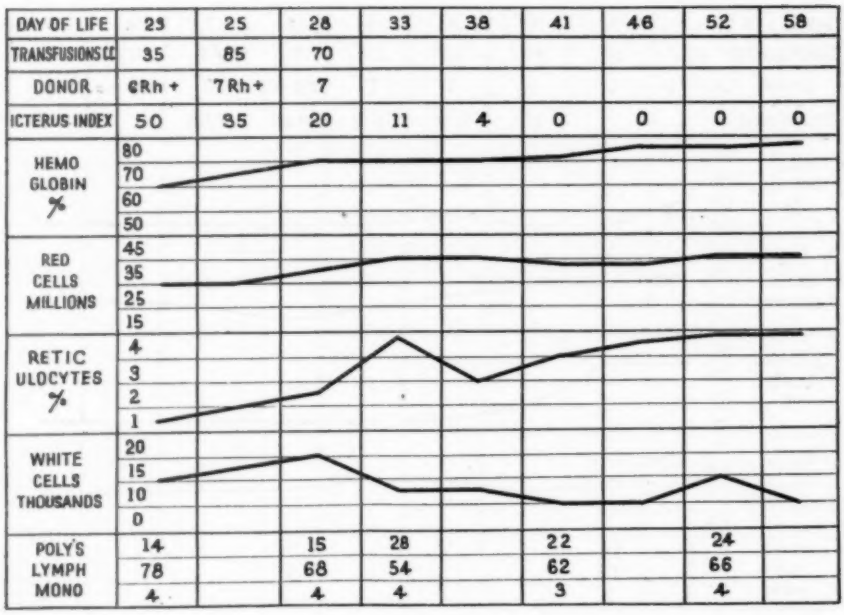

Chart III.

DISCUSSION

Inasmuch as the blood of both donor and recipient was of the same group, we were unable to demonstrate by the usual agglutination tests whether the blood of donor or recipient was hemolyzed. However, we feel that the hemolysis that occurred must have been entirely of the donor's blood, inasmuch as the recipient's blood contained the isoagglutinin, and the hemolysis ceased as soon as blood was found with which these irregular cold agglutinins did not react. This is also indicated by the fact that the red cells and hemoglobin of the infant did not appreciably fall much below their original level, and the amount of blood added by transfusions did not perceptibly increase the red cells or hemoglobin.

At first glance, a simple explanation of this experience would be that, in using the Rh-positive donors, all of the anti-Rh agglutinins that were circulating in the baby's blood, or were held by blocking antibodies, were used and recovery occurred when this was accomplished with the aid of the Rh-positive blood given after this time. When the anti-Rh agglutinins had all been used by the transfused Rh-positive blood, it would, of course, make no difference what kind of blood was then given in reference to the Rh factor. However, three Rh-positive donors were used over a period of the first week, then a change was made to an Rh-negative donor. This blood likewise resulted in the same destruction or hemolysis as shown by the failure of the red cells to increase, the continued high icterus index, and the urobilinuria. It has been known for a long time that in the treatment of these infants certain blood does not give uniformly

good results, and the hemolytic process continues. In such instances a change of donor is often beneficial. The explanation now given is that this blood was probably Rh negative, accidentally given, for formerly we were not aware of the Rh factor.

Our laboratory had reported that all of the blood given thus far was hemolyzed by the cold agglutinins existing in the infant's blood, but we had not considered that these could be a possible reason for the continued hemolysis. Inasmuch as no other factor could be found, we were about to change to type O blood when it was found that the blood of our sixth prospective donor was not hemolyzed by these cold agglutinins. When the blood was given the infant, the results were immediate as will be seen on the chart. We feel, therefore, that the Rh factor was not a part of the later hemolysis, although it was the original cause of the condition that existed at the birth of the child.

In this instance, therefore, we have a Group A_1 recipient whose blood carried isoagglutinins that clumped the cells of five Group A_1 donors at 0° C., but did not clump the same cells at 20 or 30° C. in vitro. This was in no way due to the Rh factor, because while the recipient was Rh positive, and suffered from transmitted anti-Rh isoantibodies from her Rh-negative mother, one of these donors was Rh negative and his blood was agglutinated as consistently as that of the other four Rh-positive donors. Recovery did not occur until the child was transfused with the blood of two other Group A_1, Rh-positive donors, whose blood was not agglutinated by the recipient's cold agglutinins.

As Landsteiner and Levine first pointed out, the irregular isoagglutinins in normal human sera are of four varieties: (1) those reacting with blood of subgroups A_1 and A_1B, found among individuals of subgroup A_2 and A_2B; (2) agglutinins reacting with all Group O blood, and less intensely with Group A_2; (3) all P negative individuals; and (4) unclassified, irregular isoagglutinins. The infant does not seem to fit any of the first three groups, nor have we been able to find any reference in the literature to hemolysis or agglutination occurring among Group A_1 individuals only. For this reason we have been unable to find any satisfactory explanation for this phenomena and simply report it as such. There is no other recourse except to place it in Group 4, as an irregular, unclassified isoagglutinin, contained in the blood of an A_1, Rh-positive recipient, which hemolyzed certain (five) A_1, Rh-negative and positive donors.

It has been stated that in general, immune isoantibodies are of greater significance in the severity of hemolytic transfusion reactions than natural isoantibodies. While there is a rough correlation between the titer of the isoantibodies in the in vitro tests and the severity of the reaction, serious hemolytic reactions have occurred in the absence of demonstrable isoantibodies. It would appear, as in this infant, that other properties of the isoantibodies are of greater significance than their behavior in vitro with respect to temperature. In this instance we have a severe hemolytic reaction resulting from isoantibodies in the recipient serum which have the properties of "cold agglutinins," instead of the usual hemolytic reaction, in which the antibodies behaved like "warm agglutinins."

The results of this series of transfusions show that in this type of newborn infants at least, factors other than the Rh isoagglutinins must be considered. As we have stated before, it is always well to give these infants a change of donors, even if they are group compatible, because of such irregular isoagglutinins as found in this instance.

In this respect we would like to point out again that this hemolysis caused the bilirubin to pile up in the blood stream and spill over into the tissues to such an extent that the child carried an icterus index of 470 for eleven days. This did not cause kernicterus or harm the child in any way. It has been mentioned so frequently in the recent literature, that kernicterus follows the hemolysis of blood given to these infants, or the hemolysis of the infant's blood if Rh-positive blood is given. We have not found kernicterus to be a frequent complication of this condition and do not believe that it is a necessary sequel to erythroblastosis neonatorum. The majority of reported instances show it to be associated with liver damage. We believe that the results of this case show the fallacy of the argument that any damage can be done the child by injections of either Rh-positive or Rh-negative blood.

CONCLUSIONS

An infant suffering from erythroblastosis neonatorum received transfusions from five donors of the same blood group, both of Rh-negative and Rh-positive blood. An intense hemolysis resulted from cold agglutinins in the infant's blood which reacted on the blood of these five donors. Recovery took place immediately after the blood from two Rh-positive donors was given that was not hemolyzed by the infant's cold agglutinins.

The infant completely recovered after receiving twenty-two transfusions, or a total of 2,300 c.c. of blood, over a period of thirty-three days. During this period the infant's icterus index rose to 470 and remained at this point for eleven days. This did not cause kernicterus, or harm the child in any way.

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A CASE OF STEVENS-JOHNSON DISEASE (ERYTHEMA MULTIFORME BULLOSA) TREATED WITH PENICILLIN

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THE case to be described is one of erythema multiforme bullosa, with severe mucous membrane lesions, which was treated with penicillin. We are reporting this case because we hope to point the way toward a method of treatment which will avoid eye complications in cases of erythema multiforme usually classified, because of their severity, as Stevens-Johnson disease.

This disease entity, according to Klauder[17] and Lever[4] in the United States, and many original sources elsewhere, is supposedly the erythema multiforme bullosa originally described by von Hebra[30] in 1860 and von Hebra and Kaposi[31] in 1874, with the addition of severe involvement of the oral and other mucous membranes. However, the complete entity was classified as a separate disease by Rendu[27] in 1916, and by Feissinger and Rendu[28] in 1917, who believed they were dealing with a disease not previously recognized, which they called "Ectodermosa Erosiva Pleuri-orificialis." Stevens-Johnson disease,[9] as reported in 1922, is then, only a very severe form of this condition, in which a certain proportion of patients develop eye sequelae as the most common complication.

Stevens-Johnson syndrome, as described, is a triad of skin, eye, and mucous membrane lesions, associated with marked general toxicity. The striking feature of this disease is an acute febrile condition, which occurs most commonly during spring and fall, usually in young males. Typically, there is an abrupt onset of fever, malaise, headache, and general toxicity. Simultaneously, or within twenty-four or seventy-two hours, there appears a crop of erythrematous, multiform, sometimes irislike lesions on the upper and lower extremities, and to a lesser extent, on the body and even the face. These may be macules, vesicles, or pustules.

Usually about this time there is soreness of the oral mucous membrane, and vesicles appear on the buccal mucosa which eventually become membranous lesions producing a severe stomatitis. Likewise, similar lesions appear on the other exposed mucosae, and membranes may form on the anus, as well as on the mucosa of the meatus of the penis, or on the vaginal mucosa. The child is usually prostrate. However, the most striking and serious feature of this disease is a severe conjunctivitis which invariably develops in the Stevens-Johnson syndrome. These lesions present the serious threat to the patient, whereas the remainder of the syndrome subsides completely within from three to eight weeks. The conjunctivitis in typical cases, however, in the presulfonamide days caused partial or total blindness in seven of nine cases.[9] In our tabulation of twenty-one cases

From the Service of Dr. Harry S. Altman, Department of Pediatrics, Lincoln Hospital.
This case was presented before the Pediatrics section of the New York Academy of Medicine Feb. 8, 1945.

of varying severity, only five patients received adequate doses of sulfonamide. These five recovered their sight; while seven patients, the most severe cases of the remaining sixteen (that is, those that were typical Stevens-Johnson disease), were left with total or partial blindness. Ophthalmic complications in erythema multiforme were first described by Fuchs[29] in 1876. Koke,[7] in 1941, has referred to eighteen cases, of varying intensity, untreated by chemotherapy, fourteen of which resulted in total or partial blindness. Duke-Elder[23] classifies three types of eye lesions in erythema multiforme: (1) the catarrhal, (2) the purulent, and (3) the pseudomembranous. The last two usually lead to permanent eye damage.

Fig. 1.—Photograph taken day of onset of local penicillin therapy. Photophobia is present along with purulent ophthalmic discharge. Mouth shows ulceration and crusting of tongue and buccal mucosa.

We present this case, treated vigorously with sulfonamide and penicillin, locally and systemically, in the hope that subsequent cases will be treated by one of these methods, whichever proves more efficient. We therefore hope to eliminate the specter of blindness and debilitating eye sequelae from this disease syndrome.

Whatever the cause of this condition, local or systemic, allergic, anaphylactic, toxic or bacterial, there is no doubt that the tissues of the eye are invaded

by many pyogenic organisms which can be checked by local and/or systemic antibacterial agents. Of the twenty-one cases we tabulated from the literature, sixteen patients had eye cultures, of which nine showed *Staphylococcus aureus* in pure form, six showed mixed cultures of staphylococcus and streptococcus, and only one was sterile.

REPORT OF CASE

R. M., a 9-year-old white male of Czechoslovakian ancestry, born in the United States, was admitted to the hospital on Sept. 18, 1944, with a history of toothache two weeks before admission.

Fig. 2.—Left eye closed and puffy. Right eye, forcibly opened, shows injected vessels and inflammation of the conjunctiva with a glairy purulent discharge. Eyelashes are pasted together.

Fig. 3.—Close-up of erythematous, bullous, punched-out, irislike lesion to the right of normal umbilicus (for comparison as to size).

One week before admission, the patient went swimming in a chlorinated, salt-water pool and the toothache returned. The patient was treated by local application to the gum and was relieved. That night "sores" appeared inside the mouth. A few hours before, the patient had felt weak and listless. His eyes became red and swollen. He developed photophobia. No rash was present. There was no itching. No drugs were given except an antipyretic after the onset of the systemic symptoms. There was no history of allergy or parasitic

infection. No rash was noted until one week after onset, when, because of the progression of the symptoms, he was admitted to Lincoln Hospital.

Past and family history was negative, except for familial history of rheumatic fever.

For three days before admission the patient had marked dysphagia and came to the hospital primarily because of dysphagia, photophobia, general malaise, and toxicity.

Physical Examination.—Temperature 101° F.; pulse, 120; respiration, 32; blood pressure, 110/75; weight, 59 pounds. The patient was a well-developed, well-nourished, 9-year-old white male, acutely ill, lying quietly in bed, producing large quantities of blood-tinged mucoid sputum. He was extremely toxic and without the strength to stand alone.

Skin: There were many 0.5 to 1.5 cm., round or oval, dark red, nonelevated, irislike lesions. These were mostly located on the arms and legs and also on the trunk and face. A few had small vesicles in the centers, some had already crusted over (Figs. 3, 4, and 6).

Fig. 4.—The erythematous punched-out lesions of hairy surface of arm in close-up.

Lymphatics: Several enlarged and tender anterior cervical lymph nodes.

Head: Symmetrical.

Ears: Negative.

Eyes: Eyes were held closed. The lids were swollen; there was marked chemosis and photophobia. The sclera and conjunctivae were deeply injected, with marked exudation of pus (Figs. 1, 2, and 5).

Mouth and Throat: There were bloody and dirty-gray, raised, membranous, and ulcerative lesions on the lips, buccal mucosa, margins of the tongue, and floor of the mouth. The gingivae were not affected. The membranes could be rubbed off, leaving a bleeding surface. There was extreme oral pain and tenderness. The lips had bloody encrustations and were edematous and puckered. The patient had sealorrhea, and the mouth was filled with blood-tinged mucus. The palate and uvula had small petechial hemorrhages (Figs. 1 and 5).

Nose: There was a purulent discharge from the nose. No membranes were seen.

Neck: Flaccid. No masses. Trachea in midline.

Chest: Heart negative. Lungs clear to percussion and auscultation.

Abdomen: Liver, spleen, and masses not palpable.

Extremities: Negative, except for skin.

Neurological Examination: Negative.

Rectum and Genitalia: Normal on admission. It may be noted that two days after admission, the child had not voided for twenty-four hours. It was then seen that there was an occlusive grayish membrane over the penile meatus. There was a similar membrane over the anal orifice. Both membranes were attached to the mucosa but could be removed by friction.

Fig. 5.—Crusting of lips over ulcerations. Typical facies.

Laboratory Examination.—(1) An admission eye smear showed many polymorphonuclears with large clusters of gram-positive cocci, and no intracellular organisms. A smear of the buccal mucosa showed many polymorphonuclears with many short chains of gram-positive cocci. Culture of the eyes and mouth revealed *Staph. aureus.* (2) Repeated urinalyses were negative throughout hospital stay. (3) Blood count (September 18) showed 13,600 white blood cells, and 94 per cent (13.2 Gm.) hemoglobin. Differential count revealed eosinophiles, 15; stabs, 1; polymorphonuclears, 51; basophiles, 1; monocytes, 5; and lymphocytes, 27. One week after admission the count showed 11,900 white blood cells; eosinophiles, 14; polymorphonuclears, 52; stabs, 4; and lymphocytes, 30. Ten days after admission the count was: 9,650 white blood cells; eosinophiles, 5; polymorphonuclears, 65; stabs, 1; lymphocytes, 27; and monocytes, 1. Blood Wassermann and culture were negative on admission. Stools were negative for ova and parasites. Precipitin tests, taken five months after admission, Feb. 2, 1945, for trichinosis were negative. The National Institute of Health at Bethesda,

Md., reported a negative complement fixation test for trichinosis on the same serum. There was no known allergy present.

Course.—The child was given 2 Gm. sulfadiazine on admission and 1 Gm. every four hours with double doses of soda bicarbonate. Sulfathiazole ophthalmic ointment 5 per cent was applied to the eyes. Gentian violet 1 per cent was applied to the oral lesions. Supportive therapy, infusions, sedation, etc., was given (Graph A).

Two days after admission, the child was improved generally, but there was thick purulent sputum, probably due to involvement of the trachea and upper bronchi. The conjunctivae too,

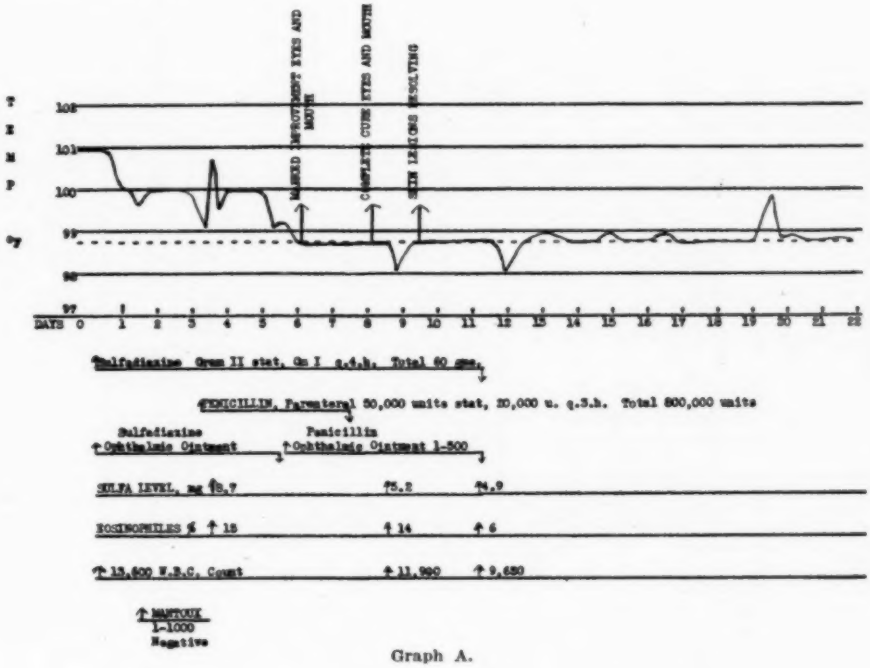
Fig. 6.—Photograph of another similar case showing skin distribution of residual pigmentation after resolution had begun.

as on admission, had marked inflammation and purulent discharge. The child's temperature was about 100° F. Since there was a possibility of the eye condition being a bacterial infection, either primary or secondary, it was decided to try penicillin therapy, because of the poor prognosis previously held for such eye cases. Struble and Bellows,[16] in 1944, presented evidence of penicillin excretion into the various tissues of the eye. Therefore 50,000 units were given, stat, parenterally, and 25,000 units every three hours thereafter, starting on the third day after admission. Five days after admission, penicillin ointment (1 ounce = 500 u.) was applied generously to the eyes and mouth every three hours. After one day of local penicillin therapy, marked improvement of the eyes and mouth was noted. Most of the conjunctivitis had cleared. There were a few grayish sloughs on the tongue and buccal mucosa. The child ate well for the first time since onset of illness. There was no marked change in the skin lesions. They cleared nineteen days after onset.

COMMENT

Although this child had received sulfadiazine and parenteral penicillin, it is noteworthy that the more marked improvement was made soon after the use of local penicillin therapy. This was a dramatic change.

According to Sutton and Sutton[15] the skin lesion in Stevens-Johnson disease heals in three to six weeks. In our study of twenty-one cases it was found that the skin cleared in at least three weeks in most cases, although one supposedly cleared in five days. In severe cases with recovery it usually takes three weeks for the eyes to clear, but in mild cases it takes only five to nine days.



Graph A.

This patient was admitted seven days after the onset of the illness. It was ten days after the onset that parenteral penicillin was started and twelve days after onset that penicillin was applied locally. After one day of local penicillin therapy, the eye and oral lesions cleared and the temperature became normal. This patient's eyes and mouth were completely normal seventeen days after the onset of the disease, and the skin was normal nineteen days after the onset. The child was untreated for the first seven days.

It must be emphasized that this patient was extremely toxic when admitted. This was a severe case and the marked recovery three days after parenteral penicillin therapy and one day after local penicillin therapy can probably be

TABLE I

CASE	REF.	MILD OR SEVERE	PER CENT EOSINOPHILES		TREATMENT AND TIME ALLOWED	TIME NECESSARY TO CURE EYES	SULFONAMIDE USED	EYE CULTURE	DID EYES CLEAR	TIME SKIN CLEARED
			ONSET	CURE						
1	1 (a)	Severe purulent	0	0	1. Metaphen 1-2500 q3h 2. Boric acid soaks 3. Atropine ointment	Began to clear in 6 days; completely clear in 9 days	No	*Staph. aureus*	Yes	
2	1 (b)	Mildly purulent	1	0	1. Boric acid soaks	18 days	No	*Staph. aureus*	Yes	
3	2		0		Sulfathiazole		Yes			
4	3	Mildly purulent	1		Symptomatic	8 days	No	*Staph. aureus;* hemolytic streptococcus	Yes	3 weeks
5	4 (a)	Severely purulent with erosions and vesicles	0	1	Symptomatic	Blind after six months	No		Blind	3 weeks
6	4 (b)	Severely purulent	0	1 and 4	1. Small; ineffective doses of sulfonamide from 26th to 30th day 2. Symptomatic	Blind (checked at 2 years)	Yes	Mixed	Blind	4 weeks with recurrence
7	5	Severe purulent with membranous lesions	1	0	1. Symptomatic 2. Local boric acid	Blind	No	*Staph. aureus*	Blind	8 weeks
8	6	Severe				Blindness and Chronic conjunctivitis	No		Blind	
9	7 (a)	Severe purulent with membranous lesions	0	0	1. Symptomatic 2. Local	30 days	No	No growth	Cleared	33 days

10	7 (b)	Mild	Normal		Neoarsphenamine	5 days	No	*Staph. aureus*	Cleared	5 days
11	7 (c)	Mild	0	0	Symptomatic	1 month	No	Not done	Cleared	1 month
12	8 (a)	Severe purulent and ulcerative	0	0	Symptomatic	Blind	No	Streptococcus; staphylococcus; Leptothrix	Blind	79 days
13	8 (b)	Severe	0	0	Symptomatic	Blind	No	Mixed	Blind	
14	9 (a)	Severe	0	2	Symptomatic	Left, blind; right, cleared in 3 weeks	No	Staphylococcus	1 blind; 1 clear	21 days
15	9 (b)	Severe			Symptomatic	Blind	No		Blind	3 weeks
16	10	Mildly purulent	0	0	Symptomatic		No	Staphylococcus	Cleared	2 weeks
17	11	Severely purulent				Inadequate data	No	Staphylococcus	Inadequate data	3½ weeks to 2 months
18	12	Severe	0	0	1. Neoprontosil 40 gr. per day for 4 days 2. Gentian violet 3. Metaphen	3 weeks; recovered	Yes	*Staph. albus*	Yes	3 weeks
19	13	Mild	0	0	Supportive	Began to clear in 8 days; cured in 3 weeks	No	Mixed	Yes	3-4 weeks
20	14	Moderately severe	0	0	1. Sulfathiazole 2. Tyrothricin for eye 3. Supportive	11 days	Yes	Mixed; predominantly staphylococcus	Yes	3 weeks
21	Case reported	Very severe	15	6	1. Sulfathiazole ophthalmic 2. Sulfadiazine 3. Penicillin local and systemic	17 days (5 days after local penicillin)	Yes	*Staph. aureus*	Yes	17 days

attributed to the antibacterial action of these agents. However, this child had been receiving sulfadiazine for five days before penicillin and this, no doubt, influenced recovery. In three previously reported cases the patients recovered on sulfonamide alone.

We cannot say whether the therapy had any effect on the skin lesions but the nineteenth day was an early date for skin resolution to occur in a severe case.

The eosinophilia herein reported had not been seen in most of the cases tabulated (Table I), although Murphy[10] recently reported a case with 6 per cent eosinophiles. A blood smear done on our patient in January, 1945, revealed 5 per cent eosinophiles still present.

On June 13, 1945, nine months after the onset of Stevens-Johnson disease, this patient was readmitted to the service with acute rheumatic polyarthritis. Whether or not there is any etiological relationship is a matter of conjecture. It is noteworthy that there is a definite familial history of rheumatic fever.

On readmission there was no sign of any recurrence or sequelae of the Stevens-Johnson syndrome in the eyes or skin. There was no eosinophilia. The child, at time of writing, had an active severe rheumatic carditis and polyarthritis.

SUMMARY

A case of a 9-year-old boy with Stevens-Johnson syndrome is presented.

1. In the past this disease in its typical, severe form was marked by but one serious sequela, that is, partial or total blindness due to eye involvement, possibly by bacterial agents. *Staphylococcus aureus* and sometimes mixed streptococcus and staphylococcus, are the most common bacteria cultured from the eye.

2. This patient was treated with sulfadiazine and penicillin, locally and parenterally, with decided improvement, which seemed to be related in dramatic time sequence to the use of penicillin, especially locally.

3. In a tabulation of twenty-one cases of erythema multiforme bullosa with mucous membrane lesions of varying severity, only five patients received adequate doses of sulfonamide or other antibacterial agents. In the seven most severe cases of the remaining sixteen, those that were typical of Stevens-Johnson disease, in which therefore, there was either purulent or membranous conjunctivitis, the patients were left with total or partial blindness.

4. It is suggested that such therapy as herein described, or modifications thereof, be used in the future to avoid eye complications. We do not know that penicillin is a "specific"; it may be, rather, an antibacterial agent useful against complications. Sulfonamides alone, in the past, prevented blindness, as did local Metaphen.

5. Six months after the onset of illness this patient was readmitted with acute rheumatic polyarthritis.

REFERENCES

1. Edgar, K. J., and Syverton, J. T.: J. PEDIAT. **12:** 151, 1938.
2. Levy, A. T.: J. Am. Dent. Assoc. **30: 1045, 1943.**
3. Low, F. B., and Davies, J. H. T.: Brit. J. Dermat. **50:** 141, 1938.
4. Lever, Walter F.: Arch. Dermat. & Syph. **49: 47, 1944.**

5. Ginandes, G. J.: Am. J. Dis. Child. **49**: 1148, 1935.
6. Barkan, H.: Arch. Ophth. **42**: 236, 1913.
7. Koke, M. P.: Arch. Ophth. **25**: 78, 1941.
8. Wheeler, J. M.: Am. J. Ophth. **13**: 508, 1930.
9. Stevens, A. M., and Johnson, F. C.: Am. J. Dis. Child. **24**: 526, 1922.
10. Murphy, R. C., Jr.: New England J. Med. **230**: 69, 1944.
11. Brigman, A.: Arch. Dermat. & Syph. **38**: 623, 1938.
12. Ageloff, H.: New England J. Med. **223**: 217, 1940.
13. Chick, F. E., and Witzberger, C. M.: Am. J. Dis. Child. **55**: 573, 1938.
14. Case Not Reported—From Records of Lincoln Hospital.
15. Sutton, Richard L., and Sutton, Richard L., Jr.: Diseases of the Skin: ed. 10, St. Louis, 1939, The C. V. Mosby Company, p. 146.
16. Struble, G. C., and Bellows, J. G.: J. A. M. A. **125**: 685, 1944.
17. Klauder, J. V.: Arch. Dermat. & Syph. **36**: 1067, 1937.
18. Caskey, C. R.: Urol. & Cutan. Rev. **36**: 370, 1932.
19. Crance, A. M.: Arch. Dermat. & Syph. **28**: 508, 1933.
20. Greenbaum, S. S.: Arch. Dermat. & Syph. **15**: 678, 1927.
21. Smith, C. A.: Tr. Univ. Michigan Pediat. & Infect. Dis. Society, 1929, p. 63.
22. Bailey, J. H.: Arch. Ophth. **6**: 362, 1931.
23. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, 1938, The C. V. Mosby Company, vol. 2.
24. Butler, J.: Arch. Dermat. & Syph. **6**: 1, 1922.
25. Stark, H. H.: Am. J. Ophth. **1**: 91, 1918.
26. Rutherford, C. W.: J. A. M. A. **93**: 1779, 1929.
27. Rendu, R.: Rev. gén. de clin. et de thérap. **30**: 351, 1916.
28. Feissinger, N., and Rendu, R.: Paris méd. **7**: 54, 1917.
29. Fuchs, E.: Klin. Monatsbl. f. Augenh. **14**: 333, 1876.
30. Von Hebra, F.: On Diseases of the Skin, London, 1866, New Sydenham Society, vol. 1. (Translated and edited by C. H. Fagge.)
31. Von Hebra, F., and Kaposi, M.: Lehrbuch der Hautkrankheiten, Stuttgart, 1874, Ferdinand Enke, p. 249.
32. Shamberg, J. F.: Diseases of the Skin and Eruptive Fever, ed. 4, Philadelphia, 1921, W. B. Saunders Company, pp. 31-37.
33. Barkan, H.: Arch. Ophth. **42**: 236, 1913.
34. Mayou, M. S.: Proc. Roy. Soc. Med. **20**: 427, 1926.
35. Osler, William: Am. J. M. Sc. **110**: 629, 1895.
36. Osler, William: Brit. J. Dermat. **12**: 227, 1900.
37. Osler, William: Am. J. M. Sc. **127**: 1, 1909.

PENICILLIN IN THE TREATMENT OF CHILDHOOD GONORRHEA

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IT IS now common knowledge that penicillin has revolutionized the treatment of gonorrhea. The sulfonamides brought about a great improvement in this same field of therapy a short time ago, but their use is by no means completely satisfactory. Penicillin, used in adequate dosage, is curative for acute gonorrhea in its various clinical forms. The existence of penicillin-fast strains of the gonococcus in acute and previously untreated infections is doubtful.

Romansky, Murphy, and Rittman[1] reported the single injection treatment of acute gonorrhea in adult males, utilizing a beeswax-peanut oil suspension. With a dose of 150,000 units there were no failures in 75 cases. When the dose was 100,000 units, 93 of 100 cases were cured and the 7 failures responded to a second dose of 150,000 units.

Sako, Tilbury, and Colley[2] reported on single-dose penicillin treatment of chronic gonorrheal vaginitis in children. In this series, the penicillin was administered as a single dose of 100,000 units dissolved in 20 c.c. of sterile saline and injected intramuscularly. There was one failure in a group of 16 cases and this one patient was "promptly cured after she received eight doses of penicillin, 10,000 units every three hours."

In a recent paper, Cutting and associates[3] discussed penicillin blood levels obtained when oral penicillin was administered with a variety of adjuvants and with enteric coatings. With these adjuvants and coatings as discussed, they treated 53 cases of acute gonorrhea, with a 72 per cent cure rate.

In the 21 cases of gonorrhea here reported, the children received from 100,000 to 300,000 units, depending on the route of administration. Only one case could be classified as really chronic, although three patients had been infected for more than three weeeks. Thirteen were cases of vaginitis and of these ten were acute cases in which no previous therapy had been administered, while three were cases that had been treated with sulfonamides without bacteriologic cure. Eight were cases of acute anterior urethritis in boys less than 10 years of age. None of these had received any previous therapy.

When the clinical picture was typical and smears showed numbers of gram-negative intracellular diplococci, treatment was begun without confirmation by positive culture. Cure was accepted in girls only after three negative smears and three negative cultures were obtained. Where possible, the last smear and culture were made six weeks after treatment. In the boys three negative smears were accepted as evidence of cure, although in all but one instance there were also one or more negative cultures.

In every patient all smears and cultures were negative after treatment. Dysuria, when present, usually subsided within twenty-four hours, and always

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TABLE I. METHODS USED IN ADMINISTERING PENICILLIN

A. *Saline Solution Intramuscularly*	
Eight girls and three boys received 100,000 units divided into six or seven equal doses, given at two-hour intervals. (Three received six doses.)	
One girl and one boy received the same amount divided into eight equal doses given at two-hour intervals.	
B. *Beeswax-peanut Oil Suspension*	
One girl and two boys received a single intramuscular injection of 150,000 units.	
One girl (chronic case, see text) received a total of 450,000 units; a first dose of 150,000 units, and a second dose, five days later, of 300,000 units.	
C. *Oral Tablets With Sodium Citrate Buffer**	
One girl (weight, 26 pounds) received 20,000 units every four hours for six doses.	
One girl (weight, 30 pounds) received 25,000 units every two hours for twelve doses.	
One girl (weight, 72 pounds) received 50,000 units every four hours for six doses.	
One boy (weight, 26 pounds) received 40,000 units every four hours for six doses.	

*These cases were treated under the supervision of Dr. Paul Gyorgy and are included through his courtesy.

within forty-eight hours. Discharge became progressively less in amount and was usually absent on the fourth or fifth day after treatment. In the boys it usually subsided in twenty-four to thirty-six hours.

In all of the cases in Table I there was prompt cure regardless of the method of administration. In the single case that qualifies as truly chronic there was a history of vaginal discharge of four months' duration. The patient had previously had at least two courses of sulfadiazine, each time followed by clinical relapse. She had also been receiving Theelin in a dosage of 5,000 units per week for three weeks. Smears were positive. She was given 150,000 units of the beeswax-peanut oil suspension, improved for a few days, and then had a recurrence of discharge. She was then given 300,000 units in the same form with prompt cure.

The single-injection use of a beeswax-peanut oil suspension of penicillin is simpler than multiple injection methods. When penicillin is plentiful and when the increased cost of the larger necessary dosage is not a factor, administration by mouth will undoubtedly be the method of choice.

SUMMARY

Twenty-one cases of gonorrhea in children were treated with penicillin by various methods of administration. Prompt cure was established in every case.

REFERENCES

1. Romansky, M. J., Murphy, R. J., and Rittman, G. E.: J. A. M. A. 128: 404, 1945.
2. Sako, W., Tilbury, R., and Colley, J.: J. A. M. A. 128: 508, 1945.
3. Cutting, W. C., Halpern, R. M., Sultan, E. H., Armstrong, C. D., and Collins, C. L.: J. A. M. A. 129: 425, 1945.

PEMPHIGUS, SUCCESSFUL TREATMENT WITH PENICILLIN

Report of a Case

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TREATMENT of pemphigus is so unsatisfactory that any therapeutic agent which results in a remission or cure is worthy of description. Any conclusion from the treatment in one patient must necessarily be guarded. We desire to report the use of penicillin in a patient with proved pemphigus, in which there has been a remission, if not a cure, over a two-year period of observation.

No attempt will be made to survey the literature concerning the myriads of therapeutic measures used in the management of pemphigus, but several recent contributions are listed for reference.

Davis and Davis,[1] Wright,[2] Wolf and Lewis,[3] Peck,[4] Greenbaum,[5] Tauber and Clarke,[6] Topping and Knofel,[7] Lever and Talbott,[8] Oppenheim and Cohen,[9] Lain and Lamb,[10] Caro,[11] and King and Hamilton[12] have used successfully various forms of arsenic, vitamins, transfusions, and/or sulfonamide in treating pemphigus.

REPORT OF A CASE

V. B. (B 16601), a 4-year-old Jewish girl, entered Duke Hospital on Oct. 24, 1943, because of generalized vesicular lesions over the body of one month's duration. The first bullous lesion was noted on the left knee. The mother opened the bulla and treated it locally with sulfathiazole ointment. Three days later the child was taken to her physician and a diagnosis of impetigo was made. She was given ultraviolet therapy on the fourth, fifth, and seventh days, despite which the lesions continued to spread over the body. At this time the mother noticed some new papular and bullous lesions. One week after onset, the patient was seen, in consultation, by a dermatologist who advised oral sulfathiazole and 10 per cent ammoniated mercury locally. The sulfathiazole was discontinued in twenty-four hours because of nausea. On the ninth day after onset, numerous new bullae appeared, which were preceded by an erythematous papular eruption. Various calamine preparations were used to allay the pruritus. The lesions continued to spread and three weeks after onset, she was seen, in consultation, by another dermatologist who confirmed the diagnosis of bullous impetigo. Therapy at this time consisted of removing the crusts with soap and water followed by applications of a mercurial ointment. New bullae appeared daily in spite of therapy, and four weeks after onset, the entire body was practically covered with new and old lesions. (Figs. 1 and 2.)

Family history and past history were noncontributory.

Physical Examination.—The temperature on admission was 37.2° C. and the pulse rate was 124. She was well developed, well nourished, and the general physical examination was entirely negative except for the skin lesions.

Laboratory Findings.—Red blood cells, 5,270,000 per cubic millimeter; hemoglobin, 100 per cent; white blood cells, 30,000 per cubic millimeter. The differential formula was as follows: polymorphonuclears, 49 per cent; eosinophiles, 23 per cent; monocytes, 2 per cent; and lymphocytes, 26 per cent. Serologic tests for syphilis were negative. X-ray examination of the lungs and heart was normal. Patch tests to 20 and 50 per cent potassium iodide were

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Fig. 1.—Showing generalized bullous eruption.

Fig. 2.—Close-up of legs demonstrating bullae arising without a surrounding zone of erythema.

negative. Urine examinations were normal. Biopsy of the skin was compatible with pemphigus.* Phytopharmacologic test was 71 per cent (normal). Cultures from the crusted lesions showed a hemolytic *Staphylococcus aureus* and beta hemolytic streptococci.

Course in Hospital.—On admission the patient was placed on treatment with 1:4,000 potassium permanganate baths, 1 per cent gentian violet solution, and 5 per cent ammoniated mercury in cremalin. She was also given a course of sulfathiazole, consisting of 0.5 Gm. every four hours for six days. There was no improvement.

One week later she was given a course of naphuride, consisting of 0.5 Gm. every day for three days, without improvement.

Three days after the last dose of naphuride, she was given 10,000 units of penicillin intravenously. The following day she was started on a course of intramuscular penicillin, receiving 5,000 units every three hours for a total dosage of 116,000 units. During the course of penicillin, the temperature spiked from 38 to 39.5° C. She improved within one week and was discharged one month from the date of admission. At discharge, there were no new bullae, the old lesions were almost completely healed, and the patient was in good health generally.

Two years after discharge the patient was in excellent health and had developed normally, both mentally and physically. There has been no recurrence of the eruption. No conclusions can be drawn from a single instance, but in a disease so serious as pemphigus a trial with penicillin seems indicated.

REFERENCES

1. Davis, W. D., and Davis, R. H.: Arch. Dermat. & Syph. 8: 627, 1923.
2. Wright, C. S.: Arch. Dermat. & Syph. 43: 145, 1941.
3. Wolf, S., and Lewis, G. M.: J. A. M. A. 116: 2017, 1941.
4. Peck, S. M.: Arch. Dermat. & Syph. 33: 150, 1936.
5. Greenbaum, S. S.: Arch. Dermat. & Syph. 41: 1073, 1940.
6. Tauber, E. B., and Clarke, G. E.: Arch. Dermat. & Syph. 40: 82, 1939.
7. Topping, M. C., and Knoefel, A. F.: J. A. M. A. 114: 2102, 1940.
8. Lever, W. F., and Talbott, J. H.: Arch. Dermat. & Syph. 43: 341, 1941.
9. Oppenheim, M., and Cohen, D.: Arch. Dermat. & Syph. 47: 40, 1943.
10. Lain, E. S., and Lamb, J. H.: Arch. Dermat. & Syph. 37: 840, 1938.
11. Caro, M. R.: Arch. Dermat. & Syph. 37: 196, 1938.
12. King, H., and Hamilton, C. M.: Arch. Dermat. & Syph. 39: 515, 1939.

*The histologic studies were concurred in by Dr. Fred D. Weidman.

POOR EATING HABITS OF THE RUNABOUT CHILD: THE ROLE OF PHYSIOLOGIC ANOREXIA

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WELL-BABY clinics, in which the examining physicians have been fellows in pediatrics of the Mayo Foundation, have been held in Rochester, Minn., for many years. Although advice concerning the general run of behavior problems has been given in these stations for a long time, we are now inaugurating a definite attempt to prevent the development, among babies, of any habit disturbances. We hope that by careful study and supervision early in life, when habits begin, we can forestall difficulties and prevent later behavior problems based on them. One clear-cut example of such a preventable habit disturbance is found in the poor eating habits of some children of the runabout age. Because such children have responded to simple measures of treatment, we thought the situation should be emphasized.

Among 360 consecutive children from 1 to 3 years of age, who were attending the well-baby clinics, the mothers of eighty-two children, or 23 per cent, reported that the children had poor appetites and would not take a sufficient quantity of food. On physical examination these children were, in general, found to be in good health and to weigh close to the average for their ages and body builds. Moreover, they did not lack energy.

As was pointed out by Bakwin and Bakwin,[1] and by Aldrich and Aldrich,[2] toward the end of the first year of life, increase in weight is much less rapid than it is during the first six months of life. Correspondingly, there is need for less food for purposes of growth in the latter part of the first year and in the next few subsequent years. This results in a physiologic waning of appetite. A mother who is accustomed to having her baby demand large quantities of food is alarmed when this demand lessens or when the demand is even replaced by the child's refusal of much of the food. The mother usually responds by undue urging. Thus, a vicious cycle is likely to be started in which the mother insists that the baby eat more than he wants and the baby refuses to comply.

Another phase of the difficulty is encountered if the mother finds that the child does not take solid food readily, she may attempt to increase the amount of more easily consumed, liquid food. Thus, milk is given in larger quantities than before and the fat content of the diet is consequently increased. Few people realize that a quart of whole milk will supply almost one-half of the total daily calories needed by the runabout child.

With these facts in mind we advised the mothers of the eighty-two children mentioned in an earlier paragraph (1) to stop forcing food, allowing the child to eat what he wanted in a reasonable, but limited, time; (2) to offer mostly the foods that the child liked without undue coaxing or threats; (3) to remove any

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food left, without comment, and to offer no more until the next meal; and (4) to give no more than approximately 1 pint (500 c.c.) of milk in twenty-four hours. In some instances we advised that the milk be skimmed.

After several months we were able to re-examine sixty-five of the eighty-two children whose appetites had been reported to be poor. It was found that fifty-nine of them, or 91 per cent, had much better appetites than before and that the mothers no longer considered that the children presented feeding problems. Only six children, or 9 per cent of the sixty-five (only 1.7 per cent of the entire group of 360), were reported to have continued to have poor appetites.

On further examination it was found that the six children just mentioned were poorly adjusted in general, did not sleep well, and presented many other behavior difficulties. It was not surprising that they should also have poor appetites and be below the expected weight. Further work is being done with these children to help solve their somewhat complicated problems.

Since such definite benefit was obtained by these simple methods of treatment in a group of children who manifested disturbance in eating habits, we felt that even more good could be accomplished by preventive measures. Therefore, we now routinely warn mothers to expect their babies, in the second year of life, to consume a reduced amount of food and we advise them not to force the babies to eat more than they desire. In a later report, we intend to give the results of this preventive effort.

SUMMARY

Among 360 children, from 1 to 3 years of age, encountered in a well-baby clinic, eighty-two (23 per cent) were reported by their mothers to be troubled with anorexia. Simple directions were given to the mothers of these children, usually in one visit only. Several months later, sixty-five of the eighty-two children were re-examined. It was then found that the anorexia of 91 per cent of the sixty-five children had been cured. The remaining 9 per cent (1.7 per cent of the entire group of 360) presented multiple behavior problems.

REFERENCES

1. Bakwin, Ruth M., and Bakwin, Harry: Psychologic Care During Infancy and Childhood, New York, 1942, D. Appleton-Century Company, Inc.
2. Aldrich, C. A., and Aldrich, Mary M.: Feeding Our Old Fashioned Children: A Background for Modern Mealtimes, New York, 1941, The Macmillan Company.

TICK PARALYSIS IN CHILDREN

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IT IS known to most physicians in the western part of the United States that tick paralysis is a dangerous disease that may prove fatal, particularly to children. Many cases of tick paralysis have been reported in the United States, but very few of these were from the eastern or central states. Since, in this country the disease is produced by two species of ticks, *Dermacentor andersoni* Stiles in the West and *Dermacenter variabilis* Say in the East, it is most prevalent in regions where these ticks are abundant. There are, however, many states where these ticks are present but in which no cases of tick paralysis have been reported. Kentucky is one such state and for this reason the following two cases are presented.

CASE REPORTS

CASE 1.—R. W., a 4-year-old white girl from Nicholas County, Ky., was admitted to the Louisville General Hospital on July 31, 1945. The chief complaint as given by her parents was that the day before admission "her legs gave away beneath her when she got out of bed." There was no pain or other complaint, but the mother noticed that when the child ate breakfast she made several ineffectual grasps before seizing objects. It was also noted that she was restless, and her pupils were thought to be large. She remained out of bed, but because the weakness of her legs had not improved she was brought to this hospital for treatment.

The past history was of interest in that the patient had a dog which was known to have had many ticks.

Physical examination revealed a well-nourished white female who was unable to stand alone but who otherwise appeared in no distress. Her temperature was 99.0° F., pulse 100, respirations 24, and blood pressure 92/60. Her hair was coarse and thick, and her skin was clear. The pupils were dilated, equal, and responded to light and accommodation. The fundi were normal and extraocular movements were intact. The neck was not stiff and no cervical masses were palpated. The following neurological findings were present: The child was unable to stand without support and would tumble forward when placed in an erect position. There was marked weakness of the lower extremities but no atrophy. Ankle and knee jerks were diminished bilaterally but abdominal reflexes were present. Asynergy of the upper extremities was noted on finger-to-nose test and on reaching for objects. Position sense and cutaneous sensibility were unimpaired.

Laboratory Examination and Course.—Complete blood count, urinalysis, sedimentation rate, blood Kahn, spinal fluid examination, Mantoux, and x-rays of chest and skull were all within normal limits.

On Aug. 1, 1945, the day after admission, there was marked weakness of the upper extremities. Biceps and triceps reflexes were diminished and ankle and knee jerks were absent. The lower extremities were completely paralyzed. No specific therapy was instituted. The next day a lumbar puncture was repeated and the pressure and the examination of the fluid were again entirely normal. Modified Kenny therapy was started but paralysis continued to progress.

On August 4, a fine papular rash appeared over face and nose and this was interpreted as miliaria rubra. The pupils were still dilated; there was complete paralysis of upper and lower extremities. Tendon reflexes were absent.

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On August 6, the child's condition was worse. The respiratory muscles, especially the intercostals, were involved and the child was restless and distressed. Paralysis of the muscles of deglutition became apparent and moderate cyanosis was present. At 11:00 A.M. she was placed into a respirator but synchronization was not satisfactory and she was removed promptly. Parenteral fluids were administered and prostigmine, 0.5 c.c. of 1:2,000 solution, was given every four hours with atropine sulfate, .15 mg. The patient was afebrile, complained of no pain, and remained mentally alert.

On August 7, an engorged tick was removed from the scalp in the occipital region. Further examination revealed enlarged occipital and cervical nodes on the right. Pupils were dilated and a right lateral nystagmus was present. All medication was discontinued.

Recovery was dramatic and within twenty-four hours the patient could walk, although the lower extremities were slightly weak. On August 9, forty-eight hours after removal of the tick, physical examination revealed only a slight weakness of the lower extremities which disappeared the following day. The tick was identified as a pregnant female, *D. variabilis*. (Fig. 1.) Patient was discharged on Aug 9, 1945.

One month later a letter from the mother reported that the child had no complaints

Fig. 1.—Tick, dorsal view.

CASE 2.*—W. M., 6-month-old white male infant whose home was Fort Knox, Ky., was admitted to the Norton Memorial Infirmary, July 12, 1943. The chief complaints as given by the parents were "general weakness and tick on the head."

The present illness began nine hours prior to admission. The child awoke at 2:00 A.M. whining and unable to take his bottle. The parents described his condition as "weak and limp all over." He was taken immediately to the Fort Knox Station Hospital where an examination revealed a large tick with its head buried in the patient's scalp. This was removed and the patient was sent home.

The patient continued to be fretful and hospitalization was thought advisable.

The past history revealed that the child had been visiting two weeks previously in Montana where Rocky Mountain Spotted Fever was prevalent. The remainder of the past history was noncontributory.

*Reported through the courtesy of Dr. M. A. Limper.

Physical examination at the time of admission revealed a well-developed child who appeared acutely ill. Skin examination was not remarkable. There was generalized flaccid weakness of the upper and lower extremities. The reflexes were not elicited and there was no stiffness of the neck. Spleen was palpable 1 cm. below the costal margin. The patient's temperature was 100.0° F. rectally.

Laboratory Examination and Course.—Blood examination revealed a white cell count of 12,200 per cubic millimeter with lymphocytes 55 per cent, and polymorphonuclear leucocytes 45 per cent; and a red cell count of 3,310,000 per cubic millimeter, with a hemoglobin of 10.2 Gm. per 100 c.c. Urinalysis was entirely negative. Lumbar puncture revealed no cells, negative globulin, 20 mg. per cent protein, 60 mg. per cent sugar and no growth on culture. Roentgenograms of the skull were interpreted as negative.

Feedings were given the first day by gavage. By 10:00 A.M. the following morning the patient was sitting up in bed playing. Temperature was never above 100.0° F. rectally. The patient was discharged June 14, 1943, fifty-four hours after admission, as entirely well.

Unfortunately the tick was not identified. Follow-up examinations to date have revealed the child to be perfectly normal.

Abbott[1] has recently made a complete review of the literature concerning paralysis produced by different species of ticks. The following discussion will be limited to the cases in the United States caused by the *D. variabilis*. This tick, the common dog tick, is found in the eastern and central states and in California. The life cycle consists of several stages of egg, larva, nymph, and adult. The incidence of the disease is greatest during the early summer months when the adult tick feeds. In the cases reported, the pregnant female tick has been found to be the causative agent. Gregson[2] and other investigators have shown experimental data to indicate that the tick injects the largest amounts of toxin on the fifth or sixth day. After ten days or less, the engorged tick drops from the host to the ground and deposits her eggs.

The first cases reported in the East due to *D. variabilis* occurred in Georgia[3] and South Carolina[4] in 1938. Since that time two more cases have been reported in each of these states[5-8] and one case each in North Carolina,[9] Texas,[10] and New York.[11]

The paralysis produced by the different species of ticks appears to be identical, however, as suggested by De Sanctis and DiSant'Agnese,[11] the prognosis may be better in those cases caused by the *D. variabilis*. In most cases the paralysis of the extremities is of the ascending type. As in Case 1, the child usually gets out of bed feeling well but discovers she is unable to walk. His efforts produce a marked ataxia and soon she is unable to stand. Ataxia of the upper extremities is also often present and unless the tick is removed the disease may progress, terminating in fatal respiratory paralysis. The pupils may become dilated and nystagmus develop. If the tick is removed before respiratory paralysis develops, recovery is usually complete and dramatic. In most cases the patient is afebrile.

As in tick paralysis produced by other species of ticks, the cases have been most frequent in female children below the age of 10 years. The site of attachment of the tick is often on the scalp, but may be beneath the breast, or in the axilla, vagina, external auditory canal, mouth, or any other exposed portion of the body.

In all but two cases reported in the United States produced by *D. variabilis* recovery has been rapid and complete following removal of the tick. Town-

send and Nash[9] reported a case in a child who died two days after the removal of the tick. Ryan and Canning[6] present a case in which weakness was present four weeks after the tick was removed.

The treatment begins with immediate removal of the tick and careful examination for multiple infestation. The tick must be removed with caution after engorgement has occurred, because there is danger of squeezing more toxin from the salivary glands into the patient. If the insect cannot be removed after killing with ether or turpentine, a small area around the site of attachment should be excised.

In Australia an antitick serum prepared from immune dogs is rather extensively used, but as yet there is none available in the United States for treatment of paralysis produced by the *D. variabilis*.

The remaining treatment is symptomatic. If respiratory paralysis is present, the patient may be placed in a respirator. However, Hamilton[12] stresses the danger of too early use of the respirator and reports a case in which death was accelerated by its use. Muscle training and massage are seldom necessary since recovery is usually complete.

Many theories concerning the cause of the paralysis have been discarded in favor of the toxin theory. As mentioned, it has been established that a neurotropic toxin is produced by the tick, but the site of production is not entirely clear.

Experiments in Australia have shown toxin to be present in saliva and eggs. Steinhaus[13] found the toxin associated with the eggs of *D. andersoni*. As yet no reports have been made in which the investigator was able to reproduce paralysis with a tick taken from a patient.

The tick, *D. variabilis*, taken from the scalp of the patient in Case 1 was intact and seven days later began to lay her eggs. About 3,000 of these eggs were ground and suspended in 1 c.c. of saline containing 200 units of penicillin. This was injected subcutaneously into a male white mouse. Twelve hours later the mouse appeared definitely sick and could not use his right foreleg. There was a collection of fluid in this region of the leg. The mouse would feed and drink but was less active than the control.

In twenty-four hours the mouse did not use his right legs and refused food. The mouse died twenty-six hours after the injection of the eggs. The control mouse, also, did not use his right front leg, apparently because of local irritation but otherwise remained active and well. In seventy-two hours no remaining involvement of the leg was noted.

Autopsy of the mouse revealed no gross abnormalities.

Five-tenths cubic centimeter of blood was removed from the dead mouse's heart and after 0.5 c.c. of saline was added, it was injected subcutaneously into another mouse. Except for local irritation the mouse's condition remained unchanged.

About twenty-one days after removal of the tick from the patient, it was placed beneath a screen on a shaved area of a young female rabbit. The tick did not feed and died two days later. The rabbit's condition remained good.

SUMMARY

1. Two cases of tick paralysis occurring in children from Kentucky are reported.

2. The flaccid paralysis that was produced in both patients disappeared rapidly after removal of the ticks.

3. In Case 1 the tick was identified as *Dermacentor variabilis* Say and its eggs were injected into a mouse producing its death.

4. In Case 2 the tick was not identified.

REFERENCES

1. Abbott, K. H.: Proc. Staff Meet., Mayo Clinic **18**: 39, 59, 1943.
2. Gregson, J. D.: Proc. Soc. Ent. Brit. Col. **33**: 15, 1937.
3. Robinow, M., and Carroll, T. B.: J. A. M. A. **111**: 1093, 1938.
4. Gibbs, J. H.: J. A. M. A. **111**: 1008, 1938.
5. Mulherin, P. A.: J. PEDIAT. **16**: 86, 1940.
6. Ryan, C. P., and Canning, H. B.: J. South Carolina M. A. **40**: 229, 1944.
7. Beach, M. W., Ravenel, B. O.: J. South Carolina M. A. **37**: 323, 1941.
8. Harper, A.: J. M. A. Georgia **31**: 442, 1942.
9. Townsend, R. G., and Nash, J. F.: South. Med. & Surg. **102**: 386, 1940.
10. Bloxsom, A., and Chandler, A. C.: Am. J. Dis. Child. **67**: 126, 1944.
11. De Sanctis, A., and Di Sant' Agnese, P. A.: J. A. M. A. **122**: 86, 1943.
12. Hamilton, D. G.: M. J. Australia **1**: 759, 1940.
13. Steinhaus, E. A.: Pub. Health Rep. **57**: 1310, 1942.

ACUTE INFECTIOUS URTICARIA

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URTICARIA is not uncommon in children and is known to arise from a wide variety of etiological factors, the most common of which is food.

A review of medical literature for the past ten years reveals reports of urticarias from almost every known food, drug, chemical, as well as heat, cold, and emotional factors; but there are only a few citing bacterial infection as the causative agent and these mention only chronic urticarias.

Leriche[1] mentions two cases of chronic urticaria with recovery after appendectomies and one following a tonsillectomy.

Hansen-Pruss[2] reports a series of ten cases of chronic urticaria in adults, one associated with pyelitis; four with upper respiratory infection; one with peridental abscess; and four from gastrointestinal infection. He reports the isolation of the hemolytic streptococcus from each case.

Eichenlaub[3] states that infection ranked second as the etiological factor in a series of fifty-eight cases of chronic urticaria.

Hopkins and Kesten[4] report fourteen cases (one, a child) of chronic urticaria associated with chronic infection.

I wish to report a series of twenty-two consecutive cases of acute urticaria in children, associated with acute infection. I have observed many such cases since this detailed study was made, but these are not included.

The syndrome is characterized by urticaria, usually with angioneurotic edema, fever, and a demonstrable focus of infection. In this series the throat was most commonly the focus, with otitis media and pyelitis accounting for the remainder.

The degree of severity of the illness varied from the acutely ill child requiring hospitalization, to the mildly ill child with one or two degrees of fever and scattered urticarial eruption lasting two or three days.

Three of the more acutely ill patients and one with the milder type of urticaria are summarized.

CASE 1.—B. E., aged three years, was seen at home with an acute throat infection for which she was given sulfonamide therapy. After two days she seemed nearly well, but on the third day she became more acutely ill than before, and I was called back to see her. Her throat showed a spider web-like membrane and there was a large macular eruption more marked around the knees and elbows but scattered irregularly over the body. She was hospitalized and because of the previous sulfonamide therapy, which was considered a possible etiological factor, the only treatment in the hospital was parenteral fluids and local treatment of the urticaria. The temperature curve ran a septic course varying from 101 to 103° F. for five days. The tongue was bright red around the margin and at the tip, and the mouth was cracked in the corners. There was considerable edema of the hands and feet. The fingers and toes were a bright cherry red early in the illness, and desquamation of fingers and toes was extensive with complete loss of all the finger and toe nails. Blood and throat cultures were negative. Blood count showed 27,000 white blood cells with no increase in eosinophiles. Urine was negative throughout.

From The Children's Memorial Hospital and the Otho S. A. Sprague Memorial Institute.

Comment.—This was the first of the series and was not recognized as infectious urticaria until later cases occurred which were very similar. This was the only case in which sulfonamide therapy preceded the rash and in the remaining twenty-one it was used to eradicate the focus of infection without any effect on the urticaria.

CASE 2.—P. A., aged 2 years, was admitted to Contagious Hospital with a diagnosis of scarlet fever. The rash was urticarial in the beginning and became confluent to show a solid red coverage of the skin. There was marked generalized edema especially of the hands and feet. The temperature on admission was 103.6° F. rectally, and gradually returned to normal on the third hospital day with sulfadiazine therapy. Physical examination was negative except for the skin and a bright red throat; laboratory data showed a blood count of 26,400 white cells, with 35 per cent eosinophiles. The blood culture was negative. The throat culture did not show hemolytic streptococci. The urine was negative. The rash and edema gradually disappeared, and there was extensive desquamation in large flakes over the entire body with many lacerations from scratching. Calamine lotion was used locally to relieve itching.

CASE 3.—M. R., aged 7 years, was seen in my office complaining of fever, a sore throat, and a rash, which was urticarial in type and more marked on the extremities and around the waist. There was marked edema of the hands and feet. Temperature was 103° F. rectally. Sulfadiazine therapy brought the temperature to normal in three days and the rash gradually subsided in ten days. White blood count was 14,300 with no increase in eosinophiles.

CASE 4.—L. B., aged 10 months, was seen in the office with fever of 100° F. rectally, and a generalized urticarial eruption. Edema of the hands and feet was evident. Physical examination disclosed an acute otitis media on the right side. Sulfadiazine cleared the infection in two days and the rash disappeared in three days.

COMMENT

Three of the more acutely ill patients and one with the milder type of urticaria have been summarized. The greater majority of the twenty-two patients were either mildly or moderately ill. The characteristic picture was an urticarial eruption of varying intensity, usually edema of the hands and feet, fever, and most commonly an infected throat. Several of the throats had a peculiar spider web-like membrane over the tonsils.

LABORATORY DATA

With the assistance of Dr. Paul Beeson of the Department of Medicine of Emory University, an attempt was made to isolate the organisms and correlate the bacteriologic findings from the throat and blood cultures. Five blood cultures were negative. Six throat cultures taken under sterile precautions did not show the same organisms in any two cultures. The hemolytic streptococcus was found in only one culture. We had planned to culture a common organism and try to show skin sensitivity, but no common organism was found.

SUMMARY

1. Twenty-two cases of acute infectious urticaria were observed between February, 1943, and May, 1944.

2. Seventeen cases associated with upper respiratory infections were seen in the winter months, October to March, inclusive.

3. Thirteen patients were males and nine were females.

4. Fourteen were under 3 years and eight from 3 to 10 years of age.

5. History of allergy was negative in eighteen, positive in three, and unknown in one.

6. Three were acutely ill; nineteen were moderately or mildly ill.

7. Nineteen urticaries were associated with acute throat infections, two with acute otitis media, and one with pyelitis.

8. The three most acutely ill had white blood cell counts of 20,000 or above, with high neutrophile counts. One had a high eosinophilia. Blood cultures were negative in five. Throat cultures showed no common organism in six instances.

9. Two of the children had second attacks, three weeks and three months later, respectively.

10. A sulfonamide was considered a possible etiological factor in one, but the rash preceded the drug in the remaining twenty-one in which it was used to clear the focus of infection with no effect on the rash. Local treatment of the rash with calamine lotion seemed much more effective than ephedrine, adrenalin, histaminase or other systemic treatment.

CONCLUSIONS

A clinical syndrome is herewith described and presented in which acute urticaria occurred in children in twenty-two cases associated with bacterial infection. It would seem that the infectious process was the etiological factor in each case.

REFERENCES

1. Leriche, R.: Presse Med. 44: 916, 1936.
2. Hansen-Pruss, O. C.: J. Allergy 9: 577, 1938.
3. Eichenlaub, F. J.: Ann. Clin. Med. 4: 170, 1925.
4. Hopkins, H. G., and Kesten, B. M.: Arch. Dermat. & Syph. 29: 358, 1934.

ENTEROGENOUS CYST OF THE ILEOCECAL REGION

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ENTEROGENOUS developmental cysts of the ileocecal region are rare. Fifty-two cases have been previously reported,[1-39] most of them in infants and children.

Congenital cysts arising from the alimentary tract have been described since 1856. The cysts may occur anywhere from the base of the tongue to the rectum, but they are most commonly found in the region of the ileocecal valve (Ladd and Gross,[37] Pachman,[34] Hughes-Jones,[40] Evans[31]). It is with such cases that this report is concerned.

Comprehensive reviews concerning congenital alimentary cysts have been made by Evans,[31] Hughes-Jones,[40] Ladd and Gross,[37] and Poncher and Milles.[41]

Enteric cysts arise from and reproduce the structure of the normal intestinal wall. They are lined by intestinal mucosa and their walls contain varying amounts of fibrous tissue and smooth muscle. They may protrude into the bowel lumen or extend outside the wall depending on whether they grow submucosally or subserosally. Attachment to the mesenteric border is common. The cavities of the cyst are unconnected with the lumen of the bowel and contain mucus.

The embryology of such cysts has been the source of considerable discussion. Enteric cysts may be isolated remnants of the omphalomesenteric or vitelline duct and are, therefore, related to Meckel's diverticula (Meckel[42]). Others believe the cysts arise from buds of endothelial tissue pinched off the primitive gut (Keibel,[43] Lewis and Thyng[44]). A third theory is that they arise from the abnormal persistence of vacuoles present in the massed cells of the solid stage in intestinal development (Bremer[45]). The first two theories explain most of the spherical cysts and diverticula, while the latter explains most of the true reduplications of the bowel.

The incidence of these cysts according to sex shows no significant predominance of females over males, although previous reports would indicate such. Of thirty-nine cases reported in which sex is given, there are twenty females and nineteen males.

Congenital ileocecal cysts occur almost exclusively in infants and children, although they have been described in adults. One report concerns a 62-year-old woman (Quensel[8]).

SYMPTOMATOLOGY

Enteric cysts may produce obstruction, pain, and bleeding. Symptoms of an acute obstruction are the most common. Less frequently there is abdominal pain either continuous or intermittent, a visible mass, constipation, and bloody stools. The latter phenomenon is rare. Often the symptoms simulate those of an acute intussusception, an acute appendicitis, or an appendicitis with abscess

From The Children's Memorial Hospital and the Otho S. A. Sprague Memorial Institute.

formation. Examination may disclose a palpable, freely movable tumor. Variable size of the mass upon subsequent examinations has been described (Rea[38]). Tenderness and rigidity over the right lower quadrant with abdominal distention may be noted.

DIAGNOSIS

The diagnosis is usually made only at the time of surgery, or at the time of autopsy. The condition has not been diagnosed accurately up to this time. Differential diagnosis in infancy should always include intussusception. Other diagnoses to consider are appendiceal abscess, regional ileitis, granuloma of the cecum, twisted ovarian cyst, mucocele of the appendix, intestinal obstruction, and volvulus. X-ray examination may or may not disclose a filling defect in the region of the ileocecal valve.

TREATMENT

Operative procedures are the accepted means of treatment. Methods advocated include resection and anastomosis with or without a safety valve ileostomy above the anastomosis, enucleation of the cyst, evacuation of the cyst contents with or without permanent drainage, marsupialization either external or internal followed by escharotics, and by-passing the region of the cyst with an enterocolostomy. Of these, resection and marsupialization are the procedures of choice. Ladd and Gross[37] favor resection when possible. The recent literature emphasizes the importance of postoperative care in the form of adequate decompression and parenteral fluids including whole blood and serum.

CASE REPORT

A 14-day-old male infant was admitted to the hospital May 23, 1945, with complaints of vomiting and bloody stools. On the day of admission he vomited his feedings and had severe hiccups. About noon he had a large, loose stool containing mucus and old blood. At 6 P.M. he had a second large, loose stool containing much bright red blood. At that time he cried as if in pain and became quiet and listless. Past history disclosed that the infant had been delivered by midforceps after a prolonged labor. The birth weight was 8 pounds, 9 ounces. He spat up part of his breast feedings while in the newborn nursery. He lost weight from birth and at the time of admission was still 6 ounces under birth weight. Physical examination revealed a fairly well-nourished male infant with a soft, thin-walled abdomen. Peristaltic waves were visible in the epigastrium. A mass about 3 cm. in diameter was visible in the right lower quadrant which on palpation was firm, movable, and very slightly tender. Rectal examination revealed good sphincter tone, but bloody mucus was passed following withdrawal of the examining finger. The patient was seen by Dr. Stanley Gibson and Dr. Harold I. Meyer who thought he had an atypical form of intussusception.

Surgery was performed by Dr. Meyer who found a hard, 2.5 cm. mass in the terminal ileum. The tumor mass lay within the lumen of the bowel and could not be enucleated. No intussusception was found. A resection of the cecum, appendix, and terminal ileum with an end-to-side ileocolostomy was done.

Postoperative treatment included decompression, parenteral blood, serum, and fluids. On the fourth day after surgery a postpyloric routine of feeding was started, but because of the ensuing distention and vomiting, oral feedings were delayed another twenty-four hours. The subsequent course was then uneventful, and the infant was discharged on June 8, 1945. At the time of writing (September, 1945) the infant was in excellent health and weighed 16 pounds.

Fig. 1.—Surgical specimen showing the cyst lying in the opened terminal ileum. The cecum and appendix are at the left.

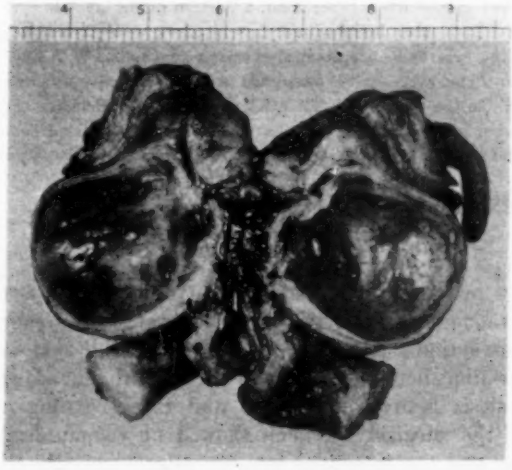

Fig. 2.—Surgical specimen showing the cyst and terminal ileum in longitudinal section. The cyst completely fills the intestinal lumen and is attached at the mesenteric border.

The pathologist reported a specimen consisting of a 4 cm. portion of terminal ileum and a 1 cm. portion of cecum with a normal appendix attached. A large obstructing cyst with a diameter of 2 cm. lay in the terminal ileum with its attachment at the mesenteric border (Fig. 1). The cyst cavity which had no communication with the bowel lumen contained glary yellow mucus. The wall of the cyst both internally and externally was smooth (Fig. 2).

Fig. 3.—Photomicrograph (×2½) of section through the cyst and ileum showing the cyst wall lined on both sides with intestinal epithelium. The cyst wall contains smooth muscle fibers and connective tissue.

Microscopic examination (Fig. 3) showed that the cyst wall was composed of smooth muscle fibers and a loose connective tissue stroma in which a few lymphocytes and an occasional polymorphonuclear leucocyte were found. At the angle of junction of the ileum and cyst the inner circular muscle fibers bifurcated, a portion going into the cyst wall and the other into the cyst base. The outer longitudinal muscle fibers were found only at the cyst base. The outer wall of the cyst had an epithelial covering continuous with and resembling that of the terminal ileum. The cyst cavity was lined with intestinal epithelium, columnar at the base, low columnar on the sides, and flattened at the apex. Beneath the epithelium at the base, the tissue had a glandular configuration with structures which resembled the Brunner's glands of the duodenum. Congestion was present throughout, and the lymphatic tissue showed hyperplasia.

Diagnosis: Congenital enterogenous cyst of the terminal ileum.

DISCUSSION

The patient presented demonstrates the difficulty of accurate diagnosis. The findings, although not entirely typical, warranted a preoperative diagnosis of acute intussusception. At operation an obstructing cyst was found in the lumen of the terminal ileum. This was resected with the adjacent bowel and a primary anastomosis between the ileum and the ascending colon was made. Examination of the surgical specimen showed no communication between the mucus-filled cyst and the intestinal lumen. Microscopically the cyst wall contained layers resembling those of the terminal ileum. The clinical, surgical, and pathologic findings in this case are comparable to those described by previous authors.

SUMMARY

1. A bibliography of reported cases of congenital enterogenous cysts of the ileocecal region is given.

2. The symptomatology, diagnosis, and treatment of these cysts are briefly summarized.

3. A case of a congenital enterogenous cyst of the terminal ileum is reported.

REFERENCES

1. Conant, N. Y.: J. Med. **16**: 82, 1856.
2. Fraenkel, E.: Virchows Arch. f. path. Anat. **87**: 275, 1882 (Gaedenchen's case, 1851).
3. Dittrich, P.: Ztschr. f. Heilk. **6**: 277, 1885.
4. Sainsbury, H.: Tr. Path. Soc. London **38**: 146, 1886.
5. Dittrich, P.: Prag. med. Wchnschr. **14**: 307, 1889.
6. Seeligmann, G.: Jahrb. d. Hamb. Staatskrankenanst (1890) **2**: 129, 1892.
7. Heuter, C.: Beitr. z. path. Anat. u. z. allg. Path. **19**: 341, 1896.
8. Quensel, U.: Nord. med. Ark. (pt. 6 no. 30) **9**: 1, 1898 (Four cases).
9. Fehleissen: Progressive Medicine, San Francisco **1**: 15, 1899 (In Evans).
10. Sprengel: Arch. f. klin. Chir. **61**: 1032, 1900.
11. Hedinger: Virchows Arch. f. path. Anat. **168**: 29, 1902 (In Evans).
12. Gfeller, L.: Deutsche Ztschr. f. Chir. **65**: 330, 1902.
13. Krogius, A.: Ztschr. f. klin. Med. **49**: 53, 1903.
14. Ayer, J. C.: Am. J. M. Sc. **131**: 89, 1906.
15. Neupert: Zentralbl. f. Chir. **37**: 714, 1910.
16. Baldwin, J. F.: M. Rec. **81**: 991, 1912.
17. Turner, P., and Tipping, H.: Proc. Roy. Soc. Med. **7**: 29, 1913.
18. Blackadar, A. D.: Tr. Am. Pediat. Soc. **25**: 296, 1913.
19. Ball, A. G.: Brit. J. Child. Dis. **11**: 259, 1914.
20. Bolton, C., and Lawrence, T. W. P.: Brit. M. J. **2**: 248, 1916.
21. Hansson, A.: Hygiea **79**: 1121, 1917.
22. Lotheisen, G.: Deutsche Ztschr. f. Chir. **179**: 394, 1923.
23. Strode, J. E., and Fennel, E. A.: Surg., Gynec. & Obst. **37**: 781, 1923.
24. MacAuley, H. F.: Brit. J. Surg. **11**: 122, 1923.
25. Aschner, P. W.: Arch. Surg. **9**: 226, 1924.
26. Bazin, A. T.: Canad. M. A. J. **15**: 130, 1925.
27. Shallow, T. A.: Ann. Surg. **81**: 795, 1925.
28. Edwards, H.: Clin. J. **57**: 319, 1928.
29. Theis, F. V.: Ann. Surg. **87**: 676, 1928.
30. Beekman, F.: Ann. Surg. **90**: 1097, 1929.
31. Evans, A.: Brit. J. Surg. **17**: 34, 1929.
32. Haggard, W. D.: S. Clin. North America **10**: 713, 1930.
33. Drennen, E.: Arch. Surg. **22**: 106, 1931 (Three cases).
34. Pachman, D. J.: Am. J. Dis. Child. **58**: 485, 1939 (Two cases).
35. Dockerty, M. B., Kennedy, R. L. J., and Waugh, J. M.: Proc. Staff Meet., Mayo Clin. **14**: 664, 1939.
36. Sawyer, C. F.: Surg., Gynec. & Obst. **70**: 78, 1940 (Two cases, one previously reported by Pachman).
37. Ladd, W. E., and Gross, R. E.: Surg., Gynec. & Obst. **70**: 295, 1940 (Eight cases).
38. Rea, C. E.: Ann. Surg. **112**: 300, 1940.
39. Rosenberg, S. A.: Ann. Surg. **119**: 873, 1944.
40. Hughes-Jones, W. E. A.: Brit. J. Surg. **22**: 134, 1934.
41. Poncher, H. G., and Milles, G.: Am. J. Dis. Child. **45**: 1064, 1933.
42. Meckel, J. H.: Tabulae Anatomico-Pathologicae, Lipsiae, 1882, J. F. Gleditsch.
43. Keibel, F.: Anat. Anz. (supp.) **27**: 39, 1905.
44. Lewis, F. T., and Thyng, F. W.: Am. J. Anat. **7**: 505, 1908.
45. Bremer, J. L.: Arch. Path. **38**: 132, 1944.

MEDITERRANEAN ANEMIA (COOLEY) IN A NEGRO GIRL

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NO CASE of Mediterranean anemia (Cooley) in a Negro has, so far as we know, been hitherto reported. The present case appears to show the essential criteria of that disease.

S. B., was admitted Feb. 16, 1945, to the Children's Ward of Stanford University Hospital, because of frequent nosebleeds and anemia. She was born Feb. 15, 1939, in Arkansas. Her mother was dark-skinned, with typical Negro features. Her father was under treatment for syphilis in the Oklahoma State Hospital for Negro Insane. The mother had one stillborn child; a son who was feeble-minded and in the same institution as the father; and three other children who were alive and well. The latter have been observed by us and were typically Negro. The mother appeared to be in good health, but no Wassermann or other test for syphilis had been taken, to her knowledge.

S. B. had been admitted previously on or about Jan. 25, 1945, to the Palo Alto Hospital because of recurrent epistaxis of three years' duration, and anemia. Her spleen was found to be greatly enlarged. The first blood count there showed: red blood cells, 3,210,000; hemoglobin, 34 per cent; white blood cells, 17,600; neutrophiles, 53 per cent; normoblasts and metamyelocytes. Another count showed red blood cells, 2,790,000; hemoglobin, 31 per cent; white blood cells, 36,200; neutrophiles, 60 per cent; normoblasts and metamyelocytes. A transfusion was given and on dismissal, about February 9, the count showed red blood cells, 3,620,000; hemoglobin, 46 per cent; white blood cells, 19,250; and neutrophiles 52 per cent. During her stay her temperature varied between 99.0° and 102.8°; she had several nosebleeds and on one occasion some bleeding from the rectum. She was referred to us for further observation.

Our physical examination revealed a somewhat thin, listless Negro girl in no apparent distress. Pulse was 128; respirations, 24; temperature, 37° C. (rectal); and blood pressure 120/65. The head and face showed normal contours for her race. In the skin were many small scars with some keloid, and a small depigmented area on the forehead. There was a generalized slight enlargement of lymph nodes. The conjunctivae were pale; the sclerae were not icteric. The oral mucous membranes were pale. The tonsils were hypertrophied. A faint systolic murmur was heard at the left sternal border; no other cardiac abnormalities were noted. There was a large umbilical hernia. The liver extended about 4 cm. below the costal margin, was soft and not tender. The spleen extended to a level a little below the umbilicus, was hard and not tender. No other physical abnormalities were detected.

Several blood counts were made, of which the following by Dr. Harry A. Wyckoff is a typical example: red blood cells, 3,700,000; hemoglobin, 8.40 Gm. per cent (49 per cent Sahli); white blood cells, 7,500; neutrophiles, 63 per cent (of which 21 per cent were banded); basophiles, 3 per cent; lymphocytes, 26 per cent; plasma cells, 2 per cent; and monocytes, 6 per cent. There were 73 nucleated red cells per 100 leucocytes. Extraordinary poikilocytosis, anisocytosis and anisochromia, polychromatia and normoblastosis were present. Target cells and pessary forms were also found. No sickling was found in sealed cover glass preparations. Van den Bergh reaction: direct, negative; indirect, 1.08 units; icterus index, 8.

From the Department of Pediatrics, Stanford University School of Medicine.

Supplementary data.—The packed cell volume was 30. The mean corpuscular hemoglobin was 25.2 micromilligrams; the mean corpuscular volume was 76 cubic micra; the mean corpuscular hemoglobin concentration was 32 per cent. Platelets numbered 260,000 per cubic millimeter. The sedimentation rate was 19 mm. per hour (Cutler). Plasma proteins amounted to 7.9 Gm. per cent. Erythrocyte fragility: hemolysis began at 5.6 per cent sodium chloride solution and was complete at 3.5 per cent, essentially duplicating a normal control. No malarial plasmodia were found after 0.3 c.c. of epinephrine was injected subcutaneously. The Wassermann and Hinton flocculation tests were negative. Fecal urobilinogen excretion was determined by Dr. Robert S. Evans to average 312 mg. daily, which is greater than the normal adult output, and indicative of a hemolytic process. The blood belonged to Group O and was Rh positive. Urine analyses were essentially negative. Repeated tests for blood in the stool were negative. Several other tests for sickling were all completely negative.

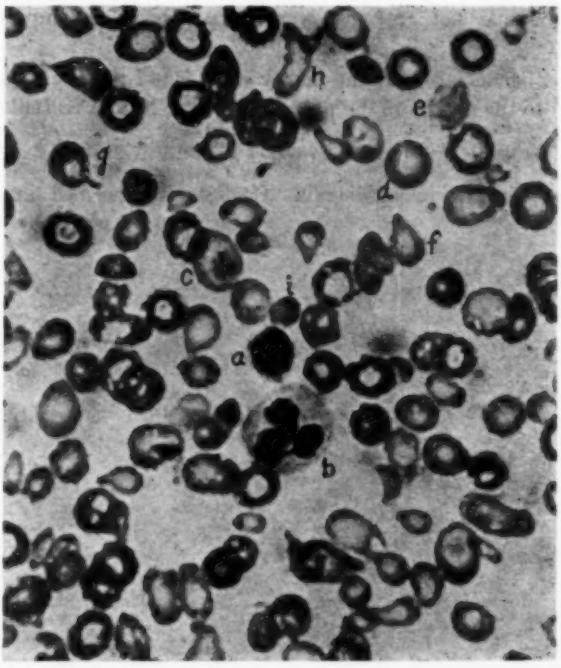

Fig. 1.—Blood smear; *a*, normoblast; *b*, granulocyte; *c*, macrocyte target cell; *d*, approximately normal erythrocyte; *e*, erythrocyte with marked irregularity of hemoglobin distribution; *f*, raindrop conformation; *g*, erythrocyte with tail; *h*, banana-shaped erythrocyte, serrated edge; *i*, microcyte.

Roentgenograms showed coarsening of bony trabeculae in the ribs, spine, pelvis, distal humeri, and bones of the hands. The skull was not, however, remarkable.

Physical examination and blood examination of the mother and two siblings living in San Francisco revealed no evidence suggestive of blood dyscrasia. Dr. E. P. Henry, Medical Superintendent of the State Hospital for Negro Insane in Taft, Oklahoma, kindly sent us blood smears from the patient's father and brother; neither of these showed abnormalities.

During her stay the patient had repeated nosebleeds. She received four transfusions without notable reaction and was dismissed March 11, 1945. At that time the red blood cells were 5,340,000 and the hemoglobin was 84 per cent (Sahli).

COMMENT

Sickle-cell anemia and spherocytic hemolytic anemia can, in our opinion, be ruled out in this case. As is evident in the accompanying microphotograph (Fig. 1), the blood was quite characteristic of Mediterranean anemia (Cooley). Morphologically, the red cells show the bizarre outlines with evidences of thinness, the irregularity of hemoglobin distribution, the tendency to fragmentation and to extreme variations in size, together with the great and persistent increase in nucleated cells (normoblasts and erythroblasts) which characterize that disease. The fragility of the erythrocytes was, however, approximately normal and did not show the increased span so often seen in Cooley's anemia. There was a moderate degree of hemolysis as shown by the fecal urobilinogen output. The bony changes, while not extreme, were of a character compatible with the disease.

Since no other members of the family were found to have a blood dyscrasia, speculation as to the origin of the patient's disease has no factual support.

SUMMARY

A case of Mediterranean anemia (Cooley) is described in a Negro girl.

EPIDERMOLYSIS BULLOSA HEREDITARIA

Report of Two Cases

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THERE are few congenital skin diseases, and of these, epidermolysis bullosa is probably the least common. Recent discovery in the Armed Forces of the persistence of this disease into adult life has occasioned a renewed interest. We have recently seen our first two cases in infants.

The first case is that of a white male infant who was brought to the outpatient department on May 2, 1944, with a history of skin lesions present since birth. No definite diagnosis had been made and treatment had been without avail. It was stated by the baby's mother that some of the earlier lesions had healed while new ones, including some in the mouth, were constantly appearing. Delivery was at full term and spontaneous, and there were no neonatal difficulties. Treatment during the first three months of life included viosterol, vitamins B and C, an evaporated milk formula, and a heat cradle. Family history for similar skin lesions was said to be negative and consanguinity of the parents was ruled out.

Physical examination when the patient was first seen by us revealed a fairly well-developed and well-nourished 3-month-old white infant with widespread bullous eruption of the skin involving the face, trunk, genitalia, and extremities. Lesions were present on the mucous membrane of the mouth. Those on the skin were pinhead to 1 inch in diameter and were in various stages (Figs. 1 and 2). Some were bullae with clear fluid while others were hemorrhagic. Some lesions were crusted and in some areas the skin was denuded. White, ulcerated patches which bled easily were present on the tongue and buccal mucosa. Except for enlargement of the pectoral and inguinal lymph nodes, there were no other positive findings. A diagnosis of epidermolysis bullosa hereditaria (dystrophia) was made and the patient was admitted to the hospital for further study.

In the differential study, serologic tests (Wassermann, Kahn, and Eagle) were repeatedly negative. Dark-field examination of fresh bleb contents and lesions in the mouth revealed no cells or organisms. Complete blood counts, on admission and since, have been entirely within normal limits. The urine has always been normal. Many cultures of fluid aspirated from the lesions were negative except for one which produced a mold growth thought to be a contaminant. Blood chemistry studies, which included nonprotein nitrogen, urea nitrogen, creatinine, chlorides, vitamin A and C levels, calcium, phosphorus, sodium and proteins were all within normal limits. The blood cholesterol varied from a low of 100 during a remission stage, to a high of 284 during a stage of exacerbation, the accepted range of the normal values being 135 to 240. The significance of these findings awaits further elucidation. (An elevated basal metabolic rate is said by some[1] to be present in this disease.) Chest x-rays demonstrated no pathology.

The patient had been on regular infant feedings on which he had maintained a fairly good state of nutrition. (His weight at 1 year was 17 pounds.) Various ointments and solutions were applied locally, including boric acid, gentian violet, potassium permanganate, ammoniated mercury, and sulfonamide ointment; all without effect. A course of sulfathiazole by mouth and 60,000 units of penicillin daily for six days failed to alter the picture. X-ray treatment with 138 roentgen units to the trunk and extremities at weekly intervals was started in January, 1945, with no apparent effect.

The course of the disease in the hospital was characterized by periods of exacerbation and remission, summer being the most unfavorable season (Figs. 3 and 4). The baby im-

From The Children's Memorial Hospital.

proved greatly during the autumn months. He was kept in a tent at 70° F., and normal room humidity, and effort made to prevent trauma by handling him as little as possible. He wore no clothing except a diaper. Sulfathiazole ointment was applied to the lesions only when secondarily infected; otherwise no local treatment was being followed at the time of writing. He lost all of his fingernails and five toenails. Nikolsky's sign (outer layer of skin rubbed off by slight trauma) was highly positive. Areas of pigmentation and scarring were present on the skin where healing occurred, and leucoplakia where healing occurred in the mouth. Skin

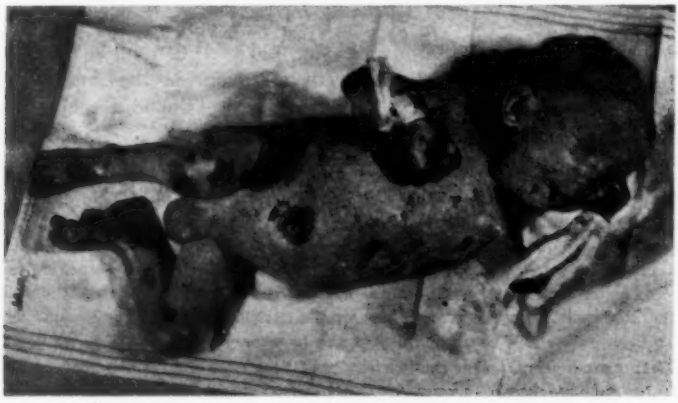

Fig. 1.

Fig. 2.

biopsy (November, 1944) revealed separation of the epidermis from the underlying tissue with only slight inflammatory reaction and loss of elastic tissue, compatible with a diagnosis of epidermolysis bullosa. Qualitative porphyria was not demonstrated.

The second case is that of a white male infant who was transferred to our hospital from Wesley Memorial Hospital where he was delivered on Sept. 30, 1944, at full term by low

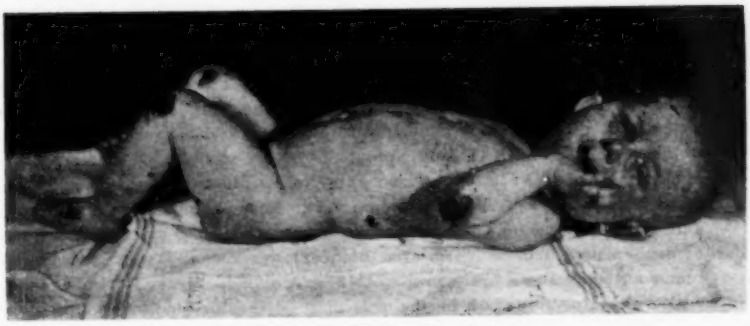

Fig. 3.

Fig. 4.

Fig. 5.

forceps. His birth weight was 6 pounds, 12 ounces. At the time of delivery some redness and denudation were noted about the bridge of the nose. On the following day, blisters appeared on the face, trunk, and extremities, and some were seen about the ear. These later broke down and crusts formed. While older lesions healed, new ones appeared. The baby was a first child and the parents were well. There was no positive history for epidermolysis bullosa, but the maternal grandmother was said to have had a skin disease all her life. Physical examination of the patient upon admission revealed a 6-week-old boy weighing only 5½ ounces above his birth weight. He did not appear ill. A few small bullae were present on the face and some were healing (Fig. 5). There were fresh scars from previous lesions on the trunk, feet, and about the penis. The nails were intact. None of the lesions were hemorrhagic and none were seen in the mouth. Nikolsky's sign was positive. The spleen was palpable. A diagnosis of epidermolysis bullosa hereditaria (simplex) was made. Blood count was normal except for mild anemia. Blood cholesterol was 121. A skin biopsy in November gave findings identical with those described in the preceding case. No qualitative prophyria was demonstrated. The baby was discharged from the hospital in December, 1944, and was followed in the outpatient department until Jan. 16, 1945, at which time he was taken to St. Louis. During this period he made an excellent gain in weight. At the time of his final visit the lesions were in a state of complete remission with scars present on the face and trunk.

The literature on epidermolysis bullosa is rather meager. The first case was described by Von Hebra in 1870, but it was not until 1886 that the name epidermolysis bullosa hereditaria was attached to this disease entity. The etiology remains obscure, though various hypotheses have been advanced. Heredity appears to play an important role and consanguinity of parents may predispose. It may occur in any race, the males being more susceptible.

The significant histopathologic change observed in almost all cases is separation of the whole of the epidermis from the corium.[3]

Typically, the disease is present at birth or appears shortly afterward. It is a chronic disease of the skin characterized by blisters which usually result from mechanical irritation. The lesions start as bullae which may be pinhead to goose egg in size and are serous, sometimes hemorrhagic. They may occur anywhere on the body but the sites of predilection are the fingers, toes, knuckles, ankles, and elbows. The lesions may rupture and crust over, in some cases leaving scars and pigmentation; often they become secondarily infected. There are exacerbations and remissions and the condition is aggravated by heat, moisture, and trauma. The disease continues throughout life, although in later life symptoms ameliorate. Occasionally puberty marks its disappearance and pregnancy may interrupt its course.

Two major types of epidermolysis bullosa are described, the "simple" and the "dystrophic."[3] The former runs a more benign course in which the lesions are seldom hemorrhagic and without involvement of mucous membranes or nails. Our first case is quite characteristic of the dystrophic type and the second of the simple type.

Porphyria has been described in some cases.[4, 5] Nikolsky's sign[1] is usually positive. The general nutritional state of the infant is not noticeably affected and prognosis for life is generally good.

The histologic changes in the skin seem to represent a quantitative change in the response of the skin to trauma, heat, and moisture.[6]

Treatment remains empiric and prophylactic.

SUMMARY

Two cases of epidermolysis bullosa hereditaria, one representing the simple type and the other the dystrophic type, have been presented. The etiology remains obscure. Empiric treatment modifies the course only slightly.

REFERENCES

1. Ludy, J. B., DeValin, C. M., and Hart, D. P.: M. Clin. North America (Feb.) 1941.
2. Rothman, S., and Henningsen, A. B.: Arch. Dermat. & Syph. 49: 284, 1944.
3. Davidson, L. T.: Am. J. Dis. Child. 59: 371, 1940.
4. Kierland, R. R., and Harrison, M. W.: Proc. Staff Meet. Mayo Clin. 15: 313, 1940.
5. Turner, W. J., and Obermayer, M. E.: Arch. Dermat. & Syph. 37: 549, 1938.
6. Greenberg, S. I.: Arch. Dermat. & Syph. 49: 333, 1944.

PITUITARY DWARFISM†

Spontaneous Correction

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THE diagnosis of anterior pituitary dwarfism is made, with but few exceptions, by the exclusion of other causes for arrested development, rather than by positive proof. The positive diagnosis of this condition by roentgenologic intra- or extrasellar tumors is rare.[1] The diagnosis is therefore a presumptive one based on the following clinical evaluations: (1) understature; (2) symmetrical proportions; (3) sexual infantilism; (4) delayed epiphyseal closure; (5) history of normal growth to about 2 to 3 years of age with sudden deceleration in rate of growth thereafter. The undersize is usually apparent by the fifth to sixth year of age.

The use of preparations of the anterior lobe of the pituitary gland, containing the growth promoting principles, in children with varying subnormal rates of growth has met with unsatisfactory results in our experience.†

We were interested in some practical and inexpensive approach to the treatment of undersized children with pituitary growth hormone. We, therefore, adopted a procedure whereby 100 c.c. of pituitary growth material were used in addition to the simultaneous administration of thyroid extract, which supposedly intensifies the action of the growth substance. The results were disappointing and most parents refused to expend further sums for treatment. In the case of a classical Lorain dwarf having a calcified intrasellar mass, approximately 1,000 c.c. of pituitary growth hormone were used with poor results. This patient received heretofore untried single high doses of 10 c.c. of pituitary growth hormone intramuscularly.

This report is concerned with a case of a seemingly spontaneous resolution of a presumptive classical hypophyseal dwarf during late adolescence, in which the girl attained a low normal height and complete sexual development. No treatment was instituted during the entire period of observation which extended from June, 1936, to February, 1942.

M. A. was first seen at the age of 12 years because she was not growing. There were no other complaints. She was born in November, 1921, to older parents of Swedish ancestry, the father being 40 and the mother 38 years of age; both were in good health. There were seven other children, all boys of good development; and their heights, as well as those of the parents, were toward the tall side. The members of the mother's and father's families were also tall. There was no family history of stunted growth or sexual disturbances.

The patient was a full-term baby weighing 6½ pounds at birth. Her height at the time of delivery was not recorded. No statural measurements were available prior to her entrance into our institution. She had been well since birth, except for measles. The dietary history was inconsequential.

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†The administration of chorionic gonadotropins in male and gonadal substances in male and female children has been accompanied by partially successful results.

When first examined, she was 46¾ inches tall and weighed 44 pounds, approximately 11 inches and 37 pounds below the averages for her age. She was a normally proportioned girl in good health. When she was 15 years old, there were no secondary sex characteristics and the external genitals were infantile although structurally complete. Rectal examination revealed a very small cervix and almost indistinguishable corpus uteri. Complete

Fig. 1.—M. A.: Age, 14½ years; weight, 54 pounds; height, 50½ inches.
Age, 20½ years; weight, 103 pounds; height, 59 inches.

endocrinological investigation was negative; nonfusion of the epiphyses was noted. Hormonal studies did not reveal any assayable estrogens or gonadotropins. At the age of 14 years and 11 months, she had a mental age of 12 years and 9 months, and an I.Q. of 89. (Weight 54 pounds, height 50½ inches.) At the age of 17 years and 4 months, her mental age was 13 years and 8 months, and her I.Q., 91.[2] She was socially and emotionally immature for her age. Her personality traits were apparently related to the physical underdevelopment. At 17 years of age there was an increase in the rate of growth, and at 22 years of age she had attained a low-normal height. (Height, 59½ inches; Weight, 94 pounds.) At 18 years of age the first secondary sex characteristics were noticed, breast enlargement being the initial change. Pubic and axillary hair appeared at 19, and menses at the age of 20 years. In 1944, when last seen at the age of 22 years, she was engaged to be married.

COMMENT

Our patient presented proportionate dwarfism, sexual infantilism, and delayed osseous development, cardinal signs present in cases conforming to classical anterior hypophyseal deficiency (Lorain type).

While statural underdevelopment is not particularly difficult to recognize, nevertheless in the diagnosis of pituitary dwarfism, other causes for retarded development must be eliminated by an exhaustive examination. It is to be emphasized that although one may be reasonably sure of the diagnosis, doubt always remains except in infrequent cases in which the hypophysis has been removed or known to be destroyed, when necropsy verifies the report, or there is roentgenologic evidence of a pituitary tumor. The diagnosis of this condition is then, with rare exceptions, a presumptive one. If there were an efficacious pituitary growth hormone, then definite and continuous response to it would constitute evidence of previous growth deficiency.

Our case illustrates progress without therapy. Had treatment been instituted, pituitary growth hormone would have been credited for the result. Although our patient presented all the criteria of deficiency of the growth and gonadotropic factors, yet she might be looked upon as a case of remarkably delayed puberty which underwent spontaneous correction.

REFERENCES

1. Bronstein, I. P., and Fabricant, N. D.: Am. J. Dis. Child. 60: 1140, 1940.
2. Foster, R., Brown, A. W., and Bronstein, I. P.: Proc. Am. A. Ment. Deficiency 63: 143, 1939.

The Academy Study of Child Health Services

THE ACADEMY STUDY

WHY A STUDY?

The Study arose from the realization, primarily on the part of pediatricians, that if children are to have the care they need in the postwar era, thorough and systematic planning to provide that care is essential. Furthermore, it is felt that the responsibility for such planning rests unquestionably on the physicians themselves. They are the ones who know what constitutes good care; they are the ones who for the most part provide that care; and they are the ones who should develop and conduct the program. But before any well-founded plans can be evolved, a study is required to determine what services are available and to evaluate the quality of those services.

One of the primary purposes of this Study is to stimulate local groups to discover for themselves the needs within their own communities and to evaluate existing facilities.

The Study is important. Unless physicians undertake the task, others less well qualified will, as indicated by various bills now before Congress.

WHAT IS IT?

The content of the Study falls into four categories:

1. *Hospital Facilities.*—Detailed information on pediatric care will be sought from all hospitals: general, pediatric, and maternity, and special hospitals such as convalescent homes, tuberculosis sanatoriums, and others.

2. *Community Health Service, Public and Private.*—The Study will cover the extent and quality of general health services such as child-health conferences, school-health service, child-guidance clinics, immunization program and public health nursing.

3. *Distribution, Qualifications, and Activities of Professional Personnel.*—Data will be collected from pediatricians, general practitioners, and specialists who care for children. Information will be sought in each community concerning availability of physicians and procedures essential for medical care, such as transfusion, provision for intravenous fluids, availability of artificial respiration and oxygen, and essential laboratory determinations.

4. *Pediatric Education.*—Basic to this Study is an evaluation of pediatric education. A study of the sixty-six medical schools throughout the country will be made to determine the quantity and quality of training in pediatrics. This division of the Study is not a part of the State Programs but will be carried out on a national basis by a special committee appointed for this purpose.

EXPECTED RESULTS

At the conclusion of the Study a report will be prepared which will be available to all who care to use it. It will be a collection of factual data which will be used by the Academy of Pediatrics as a basis upon which sound recommendations for medical care programs can be made.

CONDUCT OF STUDY

The members of the American Academy of Pediatrics are committed to carry out the Study of Child Health Services.

The responsibility for the organization and conduct of the Study within each State lies in the hands of the Academy State Chairman, who with the help of a full-time Executive Secretary will carry out the program and correlate all the many acitvities involved. However, as this is primarily a pediatric study, it is the pediatrician who is the key to the problem and it is upon his full cooperation that the success of the study depends.

NORTH CAROLINA STUDY OF CHILD HEALTH SERVICES

ARTHUR H. LONDON, JR., M.D., JOSEPH LACHMAN, M.D., AND ESTHER MILLER

With the end of the war, the American Academy of Pediatrics has instigated a nationwide Study of health and medical services for children preparatory to developing a sound program of postwar activities. It was felt that a Study, to determine "who" and "what" is currently available for the medical care of children, was the only basis on which future planning could be undertaken.

It was determined at the outset that the State would be the best unit for study and that a pilot study in one state should be conducted as a field trial prior to any large-scale planning. In selecting North Carolina as the test state several criteria were considered: geographical size which would permit rapid communication and transportation, distribution of population, sufficient facilities and services to provide a proving ground for the study but which could be examined in a period of a few months, proximity to the central office in Washington, cohesiveness of the State Pediatric Society, and willingness of the pediatricians to assume the responsibility which attends the test study of a nationwide survey.

The annual meeting of the North Carolina Pediatric Society was held at Roaring Gap on Sept. 7 and 8, 1945. Dr. Warren R. Sisson, Chairman of the Academy Committee on postwar planning, and Dr. Katherine Bain, of the United States Children's Bureau who is on loan to the Academy to assist in the study, presented the outline of the study and acquainted the pediatricians of the State with its objectives. After a free discussion those present agreed unanimously to undertake the study. A full-time executive secretary was secured; on October 15 offices were set up in Raleigh in space made available by the State Board of Health and plans for the administration of the study were prepared.

The state was divided into districts and the pediatricians located in each district were asked to assume responsibility for: (1) acquainting the physicians in the area with the purpose of the study; (2) assisting with the collection of certain hospital information; and (3) completing schedules of information concerning their own practice. A personal visit was made by the executive secretary to each pediatrician in the state during the course of which his responsibilities and duties were discussed in detail. Letters were prepared for the signature of the pediatricians who then sent them to the physicians and hospital superintendents in their districts. Pediatricians also visited the county medical societies in their respective areas at which time the meaning of the study was explained.

Following the interpretation of the study by the pediatricians to medical and hospital personnel, a general publicity campaign was started. Articles appeared in medical journals, newspapers, and the bulletins of various voluntary groups such as the State Tuberculosis Association and the state office of the National Foundation for Infantile Paralysis. An "advisory committee" of representatives of voluntary and professional organizations interested in child health was formed. A meeting of this committee was held early in the course of the study at which almost every organization represented made plans to inform their constituent local agencies of the background and purposes of the study.

When the necessary introductory work had been accomplished, the executive secretary then proceeded to send out the schedules. The pediatricians were asked to assist in the follow-up work necessary to bring in the schedules. This involved telephone calls and/or visits to public health offices, physicians, and hospital superintendents and constituted an important part of the job.

The trial schedules which were distributed in North Carolina may be described briefly as follows:

1. The schedules for hospitals included questions on the type and extent of accommodations for children, the type of staff available for treatment of different cases, the number of patients actually cared for in one day, the presence and use of laboratory services, the method of formula preparation, and the number of communicable disease cross-infections during one year. Special forms were designed to elicit information from tuberculosis, orthopedic, and nervous and mental hospitals, and also convalescent homes.

2. The questions for physicians in private practice concerned postgraduate and hospital training, designation of a specialty, availability of consultant services, and a one-day record of child patients treated. For dentists in private practice a similar schedule was prepared. The pediatrician's schedule called for more detailed information including the child and family case load, and a month's record of services to children in various age groups taking into consideration activities other than private practice.

3. The forms to be completed by local public health departments and other community health agencies were planned on a comprehensive basis. Annual data were sought on the type and number of staff, and the quantity of various services rendered children in medical well-child conferences, dental clinics, mental hygiene clinics, physically handicapped and communicable disease clinics and other school health and public health functions.

By February 15 the initial section of the study, the collection of data, had for the most part been completed. Schedules sent to the various groups have been completed and returned with the following gratifying high percentages:

QUESTIONNAIRES	PERCENTAGE OF RETURNS
Pediatric, General, and Other Hospitals	92
Special Hospitals:	
Tuberculosis	95
Orthopedic	67
Nervous and Mental	92
Convalescent Homes	100
Physicians	53
Pediatricians	92
Dentists	68
Public Health Districts	100

During the survey it has been necessary for the pediatricians in North Carolina to bear in mind the two purposes of the test study in their state: (1) to acquire data pertinent to the aims of the study, and (2) to determine the type of question which could and would be answered by professional and hospital personnel. It is believed that the majority of questionnaires returned are sufficiently complete in answers to enable statistical experts to set up adequate tabulations and meaningful analyses. On the basis of comments and suggestions received and general difficulties encountered in acquiring data on certain subjects, the schedules have been revised so that there will be less chance for misinterpretation in the future. The questions included in the schedules have been made as foolproof, self-explanatory, and simple as possible so that record-scanning and file-hunting on the part of those providing the answers are cut to the minimum. It is essential that the pediatricians accept responsibility in cooperating with the state chairman and executive secretary in the completion of the more difficult and detailed schedules.

These then are the accomplishments to date: a fairly high percentage of returns on all schedules, a high degree of completeness in the information supplied, and valuable suggestions for the revision of the questionnaires. This has been accomplished in a state which has been overstudied rather than understudied, and it has taken four and one-half months instead of the anticipated six months. Whatever else has been proved, experience in North Carolina has shown that the study can be conducted in any state with a reasonable assurance of success.

The following points based on certain experiences in this, the experimental state, may contribute to the successful administration of other state studies. Support should be sought prior to the opening of the study from all state professional groups whose members will be asked to furnish information, especially state medical and dental societies. Explanatory material should be prepared for use by these professional organizations on all levels. The fact should be emphasized that this is a study requiring the cooperation of all those who provide a facility or service for the medical care of children. This point should be stressed also by the executive secretary in his contacts with all medical, public health and hospital personnel.

General publicity directed to the state as a whole proved of great value in gaining acceptance of the study. State headquarters of all groups interested in medical care for children should be made aware of the Academy program in order to enlist support of their state and local groups. It must be borne in mind, however, that information concerning the study must reach the professional organizations first, especially the pediatricians, before any releases are made for general publicity.

Comprehensive as this study is, the data can be collected. It is a job which entails publicity, administration, coordination, personal contact, and hard work. Its success depends not on the efforts of one individual or group. Only with the cooperation of all groups solicited for data and all groups which will eventually utilize the information gathered can the study be assured of a successful conclusion.

The Social Aspects of Medicine

The following article is abstracted from a report prepared for the Children's Bureau from original Russian sources by Anna Kalet Smith.

We are indebted to the Bureau for permission to abstract the report.

HEALTH AND WELFARE SERVICES FOR MOTHERS AND CHILDREN IN THE UNION OF THE SOVIET SOCIALIST REPUBLICS

FROM ORIGINAL RUSSIAN SOURCES
BY ANNA KALET SMITH

A. Branches of the Government of the U.S.S.R. concerned with health and welfare services for mothers and children

1. *General legislative and administrative branches*

Health and welfare services for mothers and children in the U.S.S.R. (Union of the Soviet Socialist Republics) are organized on a legal basis and are administered by agencies of the Government—Federal, Republic, or local. A description of the country's legislative and administrative organization, as it relates to these services, may help to understand the operation of the system. The country's legislative and administrative machinery is prescribed in the Constitution of the U.S.S.R.

Supreme Council of the U.S.S.R.

The federal laws are enacted by the Supreme Soviet of the U.S.S.R., often called Supreme Council (which is the translation of Soviet). The composition and functions of this Council are defined in the Constitution. The Council consists of two chambers: (1) the Council of the Union, elected by citizens according to election districts and on the basis of one representative for each 300,000 inhabitants; and (2) the Council of Nationalities, elected by citizens according to certain territorial units of the country so as to give representation to the various national minorities. The members of the two Councils are elected for four years. Both Councils have equal rights.

*Council of the People's Commissars of the U.S.S.R.**

The Council of the People's Commissars of the U.S.S.R. consists of the directing heads of the various departments of the Government, such as finances, justice, public health, education, interior, trade, and industry. The members of this Council are selected by the previously-mentioned Supreme Council.

The Council of the People's Commissars of the U.S.S.R. is the executive and administrative branch of that country's Government. It issues decrees and regulations for the administration of laws enacted by the Supreme Council and watches over their enforcement, and it coordinates and directs the work of the various Government departments.

The Council of the People's Commissars is directly responsible to the Supreme Council.

Each of the sixteen republics enumerated in the Constitution, edition of 1944, as comprising the U.S.S.R. has its own Constitution, Supreme Council, and Council of People's Commissars; the composition and functions of these two bodies are in general similar to those of the U.S.S.R.

The republics constituting the U.S.S.R. are divided into provinces; some republics also have territories; others include also autonomous republics or antonomous provinces, both populated mostly by national minorities. All provinces and the larger cities are divided

*Since the preparation of the present report the use of terms "commissar" and "commissariat" has been discontinued and "minister" and "ministry" have been substituted. This took place on March 15, 1946, by resolution of the Supreme Council of the U.S.S.R.

for administrative purposes into districts. Each province, territory, provincial district, city, city district, and village is governed by a "council of workers' deputies," that is, representatives of the employed population. The council is elected for two years. The rules for the election of the members of the council are prescribed by the constitution of the individual republic. The council directs the work of the local government; it decides on the local budget; it directs the local economic and cultural activities; and takes measures for the enforcement of laws and for safeguarding the citizens' rights.

The council's executive and administrative branch is the executive committee elected by the council from among its members.

2. *Public-health authorities*

Commissariat of Public Health of the U.S.S.R.

The health work for mothers and children in the U.S.S.R. has been under the general direction of the Commissariat of Public Health since 1936, the year of the Commissariat's organization. Prior to that, the commissariats of public health of the constituent republics had charge of this work within their respective territories. The main purpose in creating this Commissariat was to coordinate health work in the various republics of the Union.

Among the functions of the Commissariat, as announced in 1938, were the direction of the public-health work, including health services for mothers and children in the entire country; the formulation of policies and standards of health work; the promulgation of rules for the administration of laws and decrees on the subjects of health; and the enforcement of this legislation.

Department of maternity care

The Commissariat of Public Health of the U.S.S.R., as reorganized in 1940, has a Department of Maternity Care.

Department of child-health services

The Commissariat's department of child-health services issues regulations for the work of various child-health services, such as children's hospitals, sanatoriums, day nurseries, child-health centers, and milk stations; it has general direction and supervision of this work and of the medical care of children in schools, kindergartens, orphanages, and other institutions.

Advisory committee and advisory council of medical men

The Commissariat of Public Health of the U.S.S.R. is assisted by an advisory committee consisting of the Commissar, the vice-commissars, a representative of the medical profession, the head of the bureau of finance of the commissariat, and one private citizen, appointed by the Commissariat. The committee meets regularly and considers, under the chairmanship of the Commissar, various phases of the commissariat's work, such as enforcement of laws, examination of reports from the local public-health branches, issuing of regulations, and appointment of staff. The decisions of the committee, if approved by the Commissar, are issued in the form of orders. In case of difference of opinion between the committee and the Commissar, the opinion of the Commissar prevails. Appeals may be taken to the Council of People's Commissars.

The Commissariat is also assisted by an advisory council of medical men without administrative responsibility, which advises the Commissariat on matters relating to public health, medical education, preventive and medical treatment, and nutrition. The council's decisions go into effect upon approval by the Commissar or the first vice-commissar.

Council on curative and preventive treatment of children and council on maternity care

Early in 1943 the Commissariat of Public Health of the U.S.S.R. issued regulations for the organization of a council on curative and preventive treatment of children as an adjunct to its own office and of similar councils at the commissariats of public health of the republics constituting the Union, and at the departments of health in provinces and territories. The purpose of these councils is to obtain the help of qualified pediatricians

in the reduction of children's morbidity and mortality. These councils examine the plans for child-health work by the above-mentioned authorities and the current problems of such work; they participate in the investigations of child-health services; they help to determine the extent of compliance with the orders of the public-health authorities; they formulate measures for checking disease among children, and take active part in conferences on child-health work. Early in 1944 one of the organs of the Commissariat of Public Health reported that such councils were operating in the majority of cities and that they, as shown by the reports of the meetings, proved very useful.

The Council on Maternity Care was appointed late in 1943 or early in 1944 by the Commissar of Public Health of the U.S.S.R. To this Council, consisting of more than 80 medical scientists and health workers, has been assigned the task of considering measures for improving maternity care and gynecological treatment.

Commissariats of public health in the republics

Each of the republics constituting the U.S.S.R. has a Commissariat of Public Health which directs and supervises the health work in the republic, including the services for mothers and children. At the head of each Commissariat is a Commissar, who is usually assisted by two or more vice-commissars, by an advisory body for administrative purposes, and by a scientific medical council. One of the vice-commissars has charge of the child-health services.

The Commissariat's advisory Committee ascertains whether the Commissariat is doing the work it is expected to do; it also examines the reports from the local health departments, and the orders issued by the Commissar. The committee's recommendations or decisions are presented to the Commissar, who issues them in the form of his own orders.

The Commissariat also has a medical council whose functions are somewhat similar to those of the council attached to the Commissariat of Public Health of the U.S.S.R.

Departments of public health in the provinces, territories, provincial districts, and cities

The provinces and territories of the R.S.F.S.R.* each have a department of public health including services for mothers and children but excluding the work of the institutions which are under the direct control of the National Government or that of the republic in which the province or territory is situated. No separate division of services for mothers and children is mentioned in the decree of 1939 on the reorganization of the departments of health.

Each of the districts into which the provinces are divided is required by law to have a department of health. One of the assistant directors has charge of the child-health work, including medical care of children in schools and in institutions.

The cities have their own departments of health; in larger cities which are divided into administrative districts, each district has such a department.

The provincial and city departments of health are supervised in administrative matters by the executive committees of the previously-mentioned councils of workers' deputies; in their medical and public-health work the departments are expected to follow the orders of the Commissariat of Public Health.

B. Health and welfare services for mothers and children

1. *General characteristics of the system*

The Russian system of maternal and child care is intended to serve all mothers and children irrespective of their status in the community. The services are provided by the Government. The private societies, which existed in the U.S.S.R. in former years, were in the course of time replaced by Government agencies. The plan of work is uniform; that is, the same method is used for the same kind of work by all institutions and agencies engaged in it; this is due to a central direction of the work by a national agency, the Commissariat of Public Health of the U.S.S.R. The services are free, on the principle of free medical care for all citizens, announced by the Constitution.

*Russian Soviet Federated Socialist Republic, the largest of the republics constituting the Union of the Soviet Socialist Republics; it occupies about nine-tenths of the Union's territory with about two-thirds of its population.

A further characteristic of the maternal and child-health work in the U.S.S.R. is the method of providing health services by district, each directed by a pediatrician. This was introduced in 1942 on the order of the Commissariat of Public Health. In this way each child is under the care of one pediatrician, except for specialists' services; this arrangement has increased the physician's sense of responsibility for the children under his care and has brought about a saving of his time; all this has resulted in improved services.

2. *Health and welfare services for mothers.* (See also section on health services in rural localities.)

Maternity clinics

Under regulations issued by the Commissariat of Public Health of the U.S.S.R. in 1938 and 1942, women receive at the maternity clinic prenatal care, care in the postnatal period, and treatment for pelvic diseases at any time.

Instruction in personal hygiene and infant care is given to the women individually at the clinic, at their places of employment, or at their homes. Informal talks, special lectures, and courses of instruction called "mothers' schools" are also provided.

Maternity homes

The Constitution of the U.S.S.R. provides for the establishment of an extensive system of maternity homes. These homes are built and equipped according to standards prescribed by the Commissariat of Public Health of the U.S.S.R. They are maintained at Government expense, with the exception of those on the collective farms.

The newborn children are separated from the mothers and placed in nurseries. The patients in the maternity homes are taught care of their own health and that of their children.

Rest homes

In large cities there are rest homes for expectant mothers and for mothers of young babies. The purpose of such homes is to enable the working woman to spend her authorized maternity leave under restful, hygienic conditions, so that she may regain her health. The women usually spend four weeks in these rest homes before childbirth and three weeks after.

3. *Health and welfare services for children*

Child-health centers in cities

At the child-health center preventive care and treatment in illness are provided for children under 4 years of age. Prior to 1943 the age limit was 3 years. Older children are cared for at the children's clinics. Pediatricians and nurses are employed at every child-health center, which as a rule serves a definite territory.

Consistent efforts are made by the center to bring under its control all newborn children in its territory. Information about births is obtained either from the maternity homes, or the registrar of vital statistics; sometimes the family itself reports the birth to the child-health center. It was reported in 1944 that in some child-health centers of Moscow, Leningrad, and other cities, 85 to 98 per cent of the newborn children in the district were under the care of a center. In some cities the percentage was much lower. Children are visited at their homes a few days after their mother's return from the maternity home, in recent years on the second or third day; in many cities, the first visits are made by physicians; in others, by nurses.

Ten to fourteen days after her discharge from the maternity home or hospital the mother is required to bring the child, if he is well, to the child-health center. If she fails to do so, a reminder is sent to her. The regulations require that the mother be given a copy of the "Booklet of the child's development," which she must read, keep, and present every time she attends a child-health center, day nursery, or hospital; she must also make certain that a notation is made in the booklet of each of her visits to the child-health center, day nursery, or hospital.

At the child-health center the physician, assisted by nurses, watches the child's development and state of health, and takes the necessary preventive measures, including immunization.

He notes his observations in the "record of development," which is kept at the center, and in the previously mentioned "Booklet of the child's development."

The public-health nurses attached to the urban child-health centers are required to visit the homes of the babies in the district. The first visit must be made not later than three days after the mother's discharge from the maternity home, and is followed by other visits at prescribed intervals. On these visits the public-health nurse is required to instruct the mother in the care of the child and of herself and to take measures for the improvement of the hygienic conditions in the home.

The reports of 26 child-health centers in the city of Moscow for 1943 showed that children less than 1 year of age were visited ten times in that year and older children twice. For other cities, the numbers varied.

The child-health center in a city is directed by a physician, who is appointed by the department of health of the city or of the city district. The department of health has general charge of the work of these centers. Sometimes a breast-milk station, or a station for the distribution of milk for children, is also a part of the center. A child-health center may be independent or combined with a maternity clinic. The child-health centers also have day beds during the summer for the treatment of children with acute diseases of the alimentary tract. Special "recovery playgrounds" are maintained at some child-health centers for children recovering from acute diseases and those suffering from rickets and from tuberculosis not requiring institutional treatment. The results of the work of these playgrounds are said to be very satisfactory.

Children's clinics

Children's clinics in cities and industrial settlements provide preventive and curative treatment for children 4 to 14 years of age. Children under 4 years of age are treated at child-health centers; those over 14 at the general clinics. This treatment includes periodic examination of school children and selection of those to be sent to recuperation homes, vacation camps, and similar institutions. In cities and industrial settlements in which no children's clinics are available, the work is done at children's divisions of general clinics; in rural localities at the rural medical stations. Children unable to come to the clinic receive medical care at their homes. Under an order of November 3, 1943, by the Commissar of Public Health of the U.S.S.R., the physician must visit a sick child at home on the same day he is called. Hospital care and treatment by specialists are also provided. Nurses employed at the clinic visit the children in their homes for the purpose of giving minor treatment, checking up whether the physicians' instructions are carried out, and instructing the mother in the care of the child.

Medical and dental care for school children

Instructions for the medical care of school children have been issued at various times by the public-health authorities. Directions for the improvement of this care were also included in the first, second, and third five-year plans for the economic reconstruction of Soviet Russia.

In 1943 the Commissar of Public Health of the U.S.S.R. called the attention of the public-health authorities to the unsatisfactory state of medical services for school children in some localities and ordered a reorganization of these services throughout the country. All children in kindergartens, schools, and institutions must now be examined twice annually and be given the necessary medical care, whether at clinics, hospitals, sanatoriums, or other institutions. In cities and industrial settlements one physician must be appointed for each 600 to 800 pre-school children (in 5 to 6 kindergartens) or 2,500 to 3,000 school children; also one nurse for each 200 to 300 children in 2 or 3 kindergartens, and 800 to 1,200 school children if they are in one school, and 700 to 800 if in 2 or 3 schools. The school physicians heretofore attached to the local public-health departments are to be transferred to the children's clinics together with the corresponding appropriations for their salaries. In the cities and towns where there are no children's clinics, the pre-school and school children will be examined and treated by other physicians on the designation of the local health authorities.

In rural localities the health work for pre-school and school children is to be done by the medical staffs of the rural clinics and rural medical stations under the direction of the pediatrician who has charge of the child-health services in the district of the province.

The Commissar ordered at the same time the appointment of a physician for each institution for children or residential school which the physician is required to visit at least three times a week in cities and at least twice a month in rural localities.

A graduate nurse must be attached to each children's institution or residential school for observing the children's health and taking preventive measures. To assure a sufficient number of nurses for this purpose the Commissar ordered the organization of a two-month course for the further training of 2,500 nurse-graduates of the Red Cross or Red Crescent courses. The public-health authorities were also directed to take measures for the health education of school children with the participation of teachers and parents. The responsibility for all this work was placed by the Commissar on the chief physicians of the local children's clinics or children's divisions of the general clinics.

Feeding of school children

Feeding of school children assumed great importance as the law on compulsory school attendance was gradually extended to all children. School feeding has come to be considered necessary to assure regular school attendance. Meals are served both in urban and rural schools.

Day nurseries

With the development of industry in the U.S.S.R., and the consequent demand for woman labor, the need for day nurseries became apparent, and the Government took steps for supplying this need. The problem of proper construction and equipment of day nurseries was considered in the preparation in 1932 of the second five-year plan for the economic reconstruction of the country, and standards for day nurseries were then prescribed.

The day nurseries are open to children between the ages of 2 months and 3 years. Older children go to kindergartens. Before admission to a day nursery the child must be examined by the pediatrician at the local child-health center. In order to prevent the spread of communicable diseases, the public-health nurse attached to the child-health center investigates the child's home. The day nurseries are divided into sections for children of different ages. A physician visits the day nursery to watch the children's health, to arrange for treatment in case of illness, and to assure the observance of the rules of sanitation and hygiene.

The day nurseries are maintained by the establishments to which they are attached—mostly by factories in cities and industrial settlements and by collective farms* in rural districts. A charge, varying with the parents' income, is made for the care of the children; a reduction is allowed for soldiers' children.

Following Germany's attack on the U.S.S.R. in 1941, when millions of women had to replace in industry the men called to the front, the day nursery came to be considered an institution of national importance. Larger funds became available for the construction of day nurseries, and in approximately one and one-half years their number (both in cities and on farms) grew 80 per cent in 35 provinces.

Among the changes necessitated by wartime conditions is the lengthening of the hours in the day nurseries; many are now open 12 to 14, even 24 hours a day, so that a child may remain there several days at a stretch. This has been found very helpful to employed mothers in case of the child's illness, or to mothers whose work takes them out of town part of the time. The Commissar of Public Health of the U.S.S.R. recently expressed himself in favor of increasing the facilities for round-the-clock care of ailing children not requiring hospitalization. Since 1941 there have been set up in many day nurseries separate sections for

*A collective farm is a cooperative organization in which the means of production and the farm buildings are the common property of the peasants constituting the collective farm; the land, which is the property of the State, is made available for the free and permanent use of the members of the collective farm. Each farmer's family is allowed to own the house in which it lives, a patch of land to cultivate for its own use, and some domestic animals. Part of the farm's crop is distributed among the collective farmers and part is sold to the Government; the proceeds from the sale are used for taxes and other expenses.

children suffering from chronic dysentery, or requiring isolation, quarantine, observation, or other attention. The children remain there for several weeks or months under medical supervision. As a result, the attendance of the registered children has improved, with a consequent decrease of loss of working time by the mothers.

At the end of 1943 it was estimated that about 45 per cent of children under 3 years of age in rural districts were cared for in permanent or seasonal day nurseries.

Institutions for children

In normal times institutions for children were organized and conducted in accordance with regulations issued in 1939 by the Commissariat of Public Health of the U.S.S.R. These institutions were intended for the following categories of children: (1) orphans who have no relatives able to care for them; (2) children of parents deprived of parental authority; (3) children of unknown parents; and (4) children whose mothers are employed as wet nurses in the institution. Children who had parents could be placed in an institution temporarily by special arrangement.

Children under 3 years of age were to be placed in separate institutions. For the purpose of better care the children were to be divided into groups of 15. Detailed rules were prescribed for the care of the children's health. Pediatricians examine all children and give treatment to those who are ill.

Recently the age limit for children in these institutions was raised to 4 years.

There are separate institutions for children between the ages of 3 or 4 and 8 years. Regulations prescribe medical and dental care for the children and facilities for their proper mental development and education. After a child reaches the age of 8 he is transferred to an institution for children of school age. There are also special institutions for physical or mental defectives and children in need of special care for other reasons. All these institutions are maintained by public funds and supervised by the local department of health.

Since the present war the importance of special protection for children in the U.S.S.R. has been stressed both by the Government and the people, particularly since the predominant majority of children have fathers or mothers in the armed forces. The devastation of the war created a need for large numbers of institutions for children. A Government decree issued in August, 1943, provides for the establishment of institutions for orphans and homeless children found in the territories liberated from the Germans prior to that time.

Foster-family care

Despite the great importance attached by the Government to institutions for children, foster-family placement has also been given a prominent place in the care of orphans and other homeless children.

4. *Health services for mothers and children in rural localities*

The Commissariat of Public Health of the U.S.S.R. has been giving particular attention to the health of the rural population. In addition to services similar to those in cities, such as child-health centers, clinics, hospitals, maternity homes, the rural districts have agencies not available in cities—intended to meet the particular needs of rural life.

The health services in the rural part of a province are supervised by the public-health inspector of the provincial department of health. Both the commissariat of public-health of each republic and the Commissariat of Public Health of the U.S.S.R. have special bureaus for the general supervision of all health work in rural localities.

Rural medical stations

Rural medical stations have been set up in the districts into which the provinces are divided. Each rural medical station serves its own territory; medical care of the population, preventive work, and sanitation are among its duties.

In cases in which the facilities of the rural medical station are insufficient to provide the necessary service, arrangements are made with a medical school, hospital, or other institution in the vicinity. Physicians from these institutions are sent to the rural station; sometimes ambulance airplanes, and medical and dental mobile clinics are sent also.

Many of these stations are equipped with clinical-diagnostic laboratories and medical libraries sent to them by the Commissariat of Public Health of the U.S.S.R.

The rural medical station is directed by a physician under the immediate supervision of the department of health of the provincial district in which it is situated. The provincial district also supplies the funds for the maintenance of the station.

Feldsher's stations

A feldsher's station is directed by a feldsher, who may be briefly described as a physician's assistant. The feldsher is a graduate of a special school with a three-year course limited to certain medical subjects; his professional field is definitely restricted. He is allowed to give first aid and treatment in minor illnesses, either at his office or at the patient's home, within the limitations imposed on his activities. More serious cases must be referred by him to a physician in the district. The feldsher inspects health conditions in the day nurseries, kindergartens, schools, and vacation camps in his district, and examines the children in these institutions.

In the localities lacking stationary physicians, the feldsher watches the well children under the general supervision of the physician in charge of the rural medical station, who visits these localities at intervals. The feldsher inspects the well children between the physician's examinations and selects for the physician's attention those who do not develop normally. He must be present at the examinations by the physician.

The feminine counterpart of a feldsher is a feldsheritsa. Large numbers of both are trained and employed in the U.S.S.R.

Sanatoriums for children on collective farms

A new kind of health agency in rural districts is the special sanatorium for children on collective farms. Such sanatoriums were set up for the first time in 1944, in several localities at the suggestion of rural physicians, who had found that many farmers' children suffering from rickets, malnutrition, and other conditions did not respond to treatment while staying at home. The children at these sanatoriums are treated by the physician stationed in the locality who is aided by graduate nurses. The sanatoriums, usually accommodating up to 40 patients, are maintained jointly by the collective farms and the official local commissions for the care of soldiers' families.

Maternity clinics in rural districts

Maternity clinics are available for expectant mothers in rural districts. Midwives or nurses stationed in the locality visit the homes of the women attending the clinics.

C. *Other activities connected with services for mothers and children*

1. *Training of personnel*

Medical training is given at the medical institute (equivalent to school of medicine in the United States). For admission to such an institute, graduation from a 10-year combined grammar-school and high-school course is required.

Some of the medical institutes have three departments each training specialists in the particular field: (1) general medical course; (2) sanitation and hygiene; (3) pediatrics. In 1941, 26 of the 72 medical institutes in the country had pediatric departments with an enrollment of 18,000 students. Pediatrics is also taught in the other medical institutes. The course in the institutes covers 5 years; for a brief period during the war of 1941-1945, it was shortened. Beginning with September, 1945, new subjects will be added, and the course will be lengthened to 6 years.

Graduates of medical institutes receive the title of physician. Those who do very good undergraduate work are permitted to study 3 more years for the degree of candidate of medical sciences. After several years of further study one obtains the highest degree, that of doctor of medical sciences. Physicians stationed in rural localities are required every three years to take not less than three months of graduate work; city physicians every five years. During their graduate study the physicians are paid their salaries in full as well as their traveling and living expenses.

Facilities for graduate study in pediatrics are available at the "scientific research institutes for the protection of mothers and infants," some of which have been renamed in recent years "pediatric medical institutes" or "research institutes of pediatrics."

In 1943 the Commissar of Public Health of the U.S.S.R. ordered the organization of refresher course for pediatricians. Also about the same time correspondence courses for graduate pediatricians were organized in Moscow. The facilities were calculated for 1,000 persons, but a larger number applied, mostly from rural localities. M. D. Kovriguina, Vice-Commissar of Public Health of the U.S.S.R. in charge of child-health services, said that much work was done in 1943 for improving the qualifications of physicians and other personnel in the child-health services, but the improvement was still insufficient.

The establishment of refresher courses for public-health personnel was ordered in 1938 by the Commissar of Public Health of the U.S.S.R. as follows: (1) One-year courses on the organization of public health for directors of city departments of health who had received no medical education and had been in their positions three years; (2) three-month courses for the vice-commissars of public health of the republics and directors and assistant directors of the provincial departments of health; (3) three-month courses for persons in responsible positions in the different branches of public health, such as child-health work, health education and medical care for the general population; and (4) three-month courses for physicians in charge of hospitals and out-patient clinics and for directors of departments of health in city districts. The commissars of public health of the constituent republics were made responsible for the enforcement of this decree.

2. *Participation of citizens' groups in the health work for mothers and children*

The agencies engaged in health or welfare work for mothers and children in the U.S.S.R. are often aided by citizens' committees or councils. The composition and functions of these groups vary according to the nature of the agency or institution to which they are attached.

The Commissar of Public Health of the U.S.S.R. ordered in 1939 the setting up of cooperating councils in connection with all out-patient clinics, hospitals, child-health centers, and other institutions for the medical treatment or preventive care of children or adults. Under the guidance of the director of the particular institution, the council is to examine the plans for the institution's work, to help in the preventive work and health education, and to decide on measures for improving the quality of the institution's services. The cooperating council is appointed by the local department of health and consists of the director of the institution, who serves as chairman, and of representatives of the institution's staff, the local department of health, the Red Cross, trade unions, and other citizens' groups. The number of members may vary between 15 and 40. The council is to meet at least once a month. The council's decisions must be put into effect by the director of the institution. In case of difference of opinion between the director and the council, the matter is referred to the local public-health authorities.

APPENDIX

1. *Labor and social-insurance legislation as it applies to mothers and children*

Industrial employment is regulated by the Labor Code. The minimum age prescribed by the Code for employment is 16 years, with exemptions permitted at the age of 14 years. However, employment at 14 years of age has become frequent since 1941 because of wartime shortage of man power.

Maternity leave is regulated by the law of July 8, 1944, on greater protection of the family. By law, nursing mothers are allowed time for nursing their children. This time is included in the hours of work. According to statements in Russian sources the protective legislation for working mothers has remained in force during the war of 1941-1945.

Social insurance is required of all persons, whether employed by the Government, cooperatives, or private organizations.

Under social insurance the workers are entitled to the following benefits:

1. Medical care;
2. Cash payments for time lost because of illness, injury, quarantine, pregnancy, childbirth, or the necessity of caring for an ill member of the family;

3. Childbirth and nursing benefits;
4. Pensions in case of permanent invalidity or old age;
5. Funeral benefits; benefits to dependents of a deceased breadwinner of the family.

Unemployment benefits were discontinued in 1930 because of the liquidation of unemployment.

To meet the cost of social insurance, the establishments or individuals employing workers are required to pay into the insurance fund a specified percentage of their payroll. The employers are prohibited by law from deducting these payments from the workers' wages or from otherwise charging them to the workers. No payments are required from the workers.

2. *School-attendance legislation*

School attendance, which was voluntary in Russia under the Czars, was made compulsory soon after the overthrow of the Czarist regime in 1917. Because of the immensity of the problem and the insufficiency of facilities needed to provide schooling for all children of school age, the Government decided to introduce compulsory school attendance gradually, making it applicable at first to the older children and extending it by degrees to the younger-age groups, first in cities and later in rural localities. In September, 1944, the application of the compulsory-school-attendance law was extended to include children 7 years of age; previously 8 years was the age for entering school.

3. *Law of July 8, 1944, on greater protection of the family*

The law of July 8, 1944, on greater protection of the family, continues a trend manifested in the law of June 27, 1936. The 1944 law provides for similar types of grants: single payments on the birth of a child and allowances for a specified period of his life. The first single payment is 400 rubles* upon the birth of the third child; the amount of this payment increases gradually to 5,000 rubles, payable upon the birth of the eleventh child and of every subsequent one.

The allowances are paid monthly for 4 years from the child's first birthday to his fifth. They begin at 80 rubles a month for the fourth child and increase gradually to 300 rubles a month for the eleventh and for every subsequent child.

The period of maternity leave for women in factories and offices—during which, under the labor and social-insurance code, their employment is prohibited and their wages paid in full—has now been extended to 35 days before childbirth and 42 days afterward.

The special taxation of unmarried persons and those married but childless, which was introduced under a decree of November 21, 1941, is now extended to married persons with fewer than three children. The tax applies to men from 20 to 50 years of age and to women from 20 to 45. For a person subject to general-income tax this special tax will be 6 per cent of his income if he is childless; 1 per cent if he has one child.

The mother of a child born out of wedlock is deprived of the right to seek court action for the establishment of paternity and for obtaining support from the child's father; also, she is required to give her own surname to the child.

Stringent rules regarding divorce are prescribed in the new law, which requires court action according to a definite procedure. Under the law of 1936 the only requirement was that both parties appear before the local registrar of vital statistics.

The law of 1936 introduced, as a possible deterrent to divorce, a fee of 50 rubles for the first divorce, 150 rubles for the second, and 300 for the third and any subsequent one. Now a payment of 100 rubles is required at the time of filing the petition; and the fee for the divorce itself, payable by one of the parties or jointly by both, varies, at the discretion of the court from 500 to 2,000 rubles, a price considered prohibitive for the average person.

4. *Institutes of research in pediatrics, obstetrics, and gynecology*

The institutes of pediatric research are centers for the study of problems relating to the prevention of disease among children, improvement of diagnosis, reduction of mortality,

*The nominal foreign-exchange value of a ruble was 20 cents before 1940; its present value is not quoted.

and development of other methods of safeguarding child health. To this end investigations are made at the institutes of the more prevalent children's diseases. Statistics of children's morbidity and mortality are analyzed; standards are formulated for children's hospitals, clinics, and health centers, and for other child-health and welfare services; advice and information are given to various institutions and agencies; and popular literature is published. There are also institutes of obstetrics and gynecology.

Formerly the institutes of pediatric research and those of obstetrics and gynecology were combined into "institutes for the protection of mothers and infants." In some localities such institutes are still in existence.

All these institutes collaborate with the various health agencies and give them systematic advice in their work. The institutes also have facilities for training pediatricians, obstetrician-gynecologists, and nurses for the health services. The extent of the institutes' activities varies considerably and depends, among other things, on the territory served by the individual institute. A few of the institutes are federal and serve the entire country; others belong to the republics constituting the U.S.S.R.; the remainder are provincial or municipal. They are all under the general supervision of the Commissariat of the Public Health of the U.S.S.R.

Twenty-three institutes were operating in the U.S.S.R. before 1941. Several of them stopped their work when their buildings and equipment were destroyed by the invading Germans in 1941 and 1942; however, some were rebuilt as the territories were gradually reconquered by the Russians.

One of the most important institutes because of the large scale of its research and teaching activities is the Leningrad State Pediatric Medical Institute, established in 1925 under the name of "Leningrad Scientific Institute for the Protection of Mothers and Infants"; in 1935 it was given its present name.

Some of the Institute's functions are as follows:

1. Theoretical and practical study of the anatomy, physiology, psychology, hygiene, dietetics, and pathology of the infant and young child.
2. Study of various forms of child-health services and decision on measures for their improvement.
3. Information and advice to public and private agencies and to individuals on the subjects relating to the Institute's work.
4. Training of physicians and nurses for child-health services.
5. Preventive and curative treatment of children.

For the study of the physiology of the well child the Institute has a separate department with accommodations for more than 100 newborn children, babies under 1 year of age, and older children. In another department are studied the diseases peculiar to infancy and early childhood, also venereal diseases, diseases of the nerves, and others; there is also a surgical clinic. In a dispensary treatment is given to children for various diseases, including tuberculosis, diseases of the skin, eye, ear, nose, and throat, and others; dental care is also provided.

The Institute has a department of physiotherapy, an x-ray department, a milk and dietetic station, and numerous laboratories and shops for the preparation of technical instruments; there are also exhibits on child care, and a library with a reading hall.

Another phase of the Institute's work is the training it provides for physicians and nurses who intend to enter the child-health services. For this purpose the Institute has departments in which instruction is provided in such subjects as health services for infants and children; physiology, hygiene, and dietetics of infancy; pathology of infancy; surgical pediatrics; and venereal disease. There is also a school for the training of nurses. Numerous reports have been published by the Institute.

News and Notes

Many Fellows are not familiar with the Tumor Registry Committee of the Academy. Dr. Harold W. Dargeon, 1095 Park Avenue, New York 28, is Chairman and associated with him are Drs. Herbert F. Jackson and Hayes Martin of New York.

Dr. Willis J. Potts, who has been a member of the surgical staff of the Children's Memorial Hospital in Chicago since 1931, will become head of the department of surgery on April 1, 1946. Dr. Albert H. Montgomery, who was formerly in charge, will remain as consulting surgeon.

The Pediatrician and the War

The following Fellows have been released from service:

Dr. Louis Appel, Flushing, N. Y.
Dr. Barnett P. Briggs, Little Rock, Ark.
Dr. George W. Caldwell, New York, N. Y.
Dr. Nathan H. Einhorn, Yeadon, Pa.
Dr. R. Bruce Eldredge, Los Angeles, Calif.
Dr. Herbert L. Elias, Rockville Center, L. I., N. Y.
Dr. Harry H. Gordon, New York, N. Y.
Dr. Raymond F. Grisson, Oak Park, Ill.
Dr. Wesley R. Heard, Pasadena, Calif.
Dr. Richard C. Hiestand, Springfield, Ohio
Dr. Alvin H. Jacobs, San Francisco, Calif.
Dr. Robert M. Keagy, Altoona, Pa.
Dr. George N. Leonard, Miami Beach, Fla.
Dr. Albert U. Peacock, Hartford, Conn.
Dr. Samuel X Radbill, Philadelphia, Pa.
Dr. Thomas F. Reilly, Springfield, Mass.
Dr. W. Pierre Robert, Beaumont, Texas
Dr. Hulda E. Thelander, San Francisco, Calif.
Dr. Walter M. Whitaker, Quincy, Ill.
Dr. Byron P. York, Houston, Texas

The following promotions have been reported to the JOURNAL:

Major Harry H. Gordon to Lieutenant Colonel
Lieutenant Commander Milton Kurzrok to Commander
Lieutenant Commander Thomas F. Reilly to Commander
Major Samuel P. Wainwright to Lieutenant Colonel